(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 220 865 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **29.07.92**

(51) Int. Cl.[5]: **C07K 5/06**, C07D 227/087, A61K 37/02

(21) Application number: **86307853.1**

(22) Date of filing: **10.10.86**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Lactam derivatives, their preparation and their use as hypotensive agents.**

(30) Priority: **11.10.85 JP 226044/85**

(43) Date of publication of application:
06.05.87 Bulletin 87/19

(45) Publication of the grant of the patent:
29.07.92 Bulletin 92/31

(84) Designated Contracting States:
AT BE CH DE ES FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 046 291
EP-A- 0 046 292
EP-A- 0 142 335

CHEMICAL ABSTRACTS, vol. 101, 1984, page 262, abstract no. 86217q, Columbus, Ohio, US; E.D. THORSETT et al.: "Conformationally restricted inhibitors of angiotensin converting enzyme", & PEPT.: STRUCT. FUNCT., PROC. AM. PEPT. SYMP., 8TH 1983, 555-8

(73) Proprietor: **SANKYO COMPANY LIMITED**
No. 1-6, 3-chome Nihonbashi Honcho Chuo-ku
Tokyo(JP)

(72) Inventor: **Yanagisawa, Hiroaki c/o Sankyo Chem. Res. Labs.**
Sankyo Co. Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: **Ishihara, Sadao c/o Sankyo Chem. Research Labs.**
Sankyo Co. Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: **Ando, Akiko c/o Sankyo Chem. Res. Labs.**
Sankyo Co Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: **Kanasaki, Takuro c/o Sankyo Chem. Res. Labs.**
Sankyo Co Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: **Koike, Hiroyuki c/o Sankyo Biol. Res. Labs.**
Sankyo Co Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)
Inventor: **Iyima, Yasuteru c/o Sankyo Biol. Res. Labs.**
Sankyo Co Ltd. 2-58, 1-chome, Hiromachi Shinagawa-ku Tokyo(JP)

EP 0 220 865 B1

(74) Representative: **Gibson, Christian John Robert et al**
MARKS & CLERK 57/60 Lincoln's Inn Fields London WC2A 3LS(GB)

Description

The present invention relates to a series of lactam derivatives which have the valuable ability to lower blood pressure and which are hence of potential use in the treatment of humans and other animals suffering from elevated blood pressure.

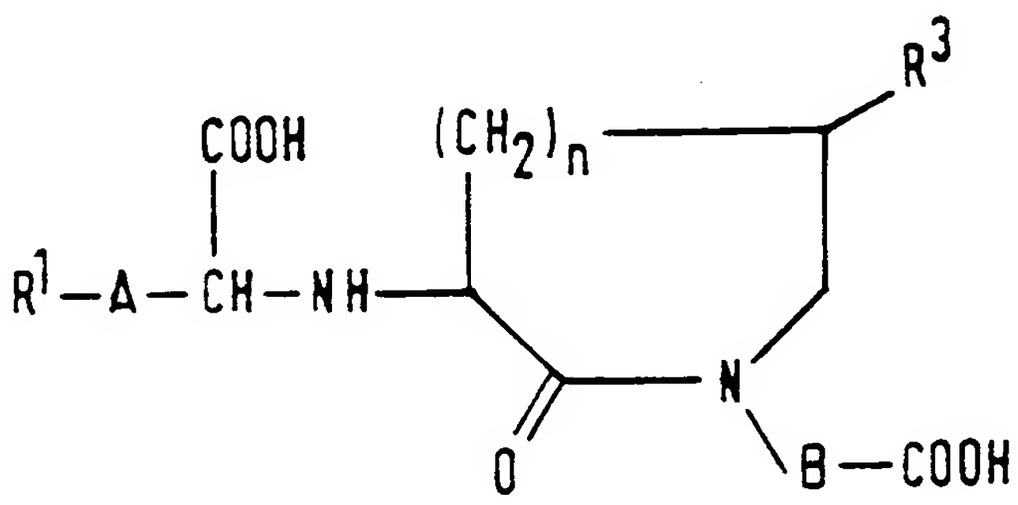
There is considerable evidence that reduction of elevated blood pressure reduces the risks of morbidity and mortality. Elevated blood pressure (hypertension) can be caused by a variety of factors and a large number of drugs is available for the treatment of hypertension, the drug of choice being dictated in large measure by the cause of the hypertension, as well as the degree of hypertension and the acceptance of the treatment by the patient. One of the known causes of hypertension is the presence in blood plasma of the polypeptide known as angiotensin II, and a reduction in the blood plasma levels of angiotensin II has been shown to reduce hypertension. The first step in the production of angiotensin II in the mammalian body is the conversion of a blood protein, by the enzyme renin, to a polypeptide known as "angiotensin I". This angiotensin I is then converted by angiotensin converting enzyme (hereinafter referred to, as is conventional, as "ACE") to angiotensin II. The enzyme ACE has another metabolic function, namely it participates in the metabolism of bradykinin, a natural vasodilator, converting it to an inactive metabolite.

Hence, the enzyme, ACE, is capable of raising blood pressure by two routes: one is the production of angiotensin II, which itself raises blood pressure; the second is the inactivation of bradykinin which, through its vasodilatory activity, tends to reduce blood pressure. There has, therefore, been considerable interest in recent years in the development of compounds having the ability to inhibit the activity of ACE.

We have now discovered a series of lactam derivatives which have this ability. The compounds of the invention have either 6, 7 or 8 ring atoms in the lactam system and can thus be regarded as 1,3,5-trisubstituted piperidin-2-one derivatives, 1,3,6-trisubstituted perhydroazepin-2-one derivatives or 1,3,7-trisubstituted perhydroazocin-2-one derivatives, according to whether they have 6, 7 or 8 ring atoms.

The closest prior art is believed to be represented by European Patent Publication No. 46,291, European Patent Publication No. 46,292 and Chem. Abst. 101, (1984) 86217q, each of which discloses a series of perhydroazepin-2-one (or caprolactam) derivatives having substituents at the 1- and 3-positions and optionally also having a substituent at the 7-position. The compounds of these disclosures, however, unlike the compounds of the present invention, are unsubstituted at the 6-position. Surprisingly, we have found that the compounds of the present invention have several advantages over the prior art compounds of the above mentioned documents, including a higher ACE inhibitory activity and a longer duration of this activity in vivo.

The compounds of the invention are those compounds of formula (I):



(I)

in which:

R^1 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_6-C_{14} aryl group or a heterocyclic group having from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and (b);

R^3 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, an aralkyl group wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl, a C_6-C_{14} aryl group, a C_1-C_6 alkyl group having a heterocyclic substituent or a heterocyclic group, where said heterocyclic group or said heterocyclic substituent has from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and (b);

A represents a single bond, a methylene group, an ethylene group or a group of formula -CO-CH_2-, -O-CH_2- or -S-CH_2-;
B represents an alkylene group having from 1 to 4 carbon atoms; and
n is an integer from 1 to 3;

substituents (a):

hydroxy groups, C_1-C_6 alkoxy groups, C_6-C_{10} carbocyclic aryl groups having from 0 to 3 of substituents (a) and/or (b), aralkyloxy groups where the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b), C_6-C_{10} aryloxy groups, halogen atoms, nitro groups, cyano groups, carboxy groups, alkoxycarbonyl groups having a total of from 2 to 7 carbon atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups wherein each alkyl part is C_1-C_6 alkyl, aliphatic or carbocyclic aromatic carboxylic acylamino groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1-C_6 alkyl, dialkylcarbamoyl groups where each alkyl part is C_1-C_6 alkyl, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups and C_6-C_{10} carbocyclic arylsulphonyl groups wherein the aryl part has from 0 to 3 C_1-C_6 alkyl substituents;

substituents (b):

C_1-C_6 alkyl groups and aralkyl groups wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b);
and pharmaceutically acceptable salts and esters thereof.

The invention also provides a pharmaceutical composition for the treatment of angiotensin-induced hypertension, which composition comprises a hypotensive agent in admixture with a pharmaceutically acceptable carrier or diluent, wherein said hypotensive agent is at least one compound of formula (I) or a pharmaceutically acceptable salt or ester thereof.

The invention still further provides the use for the manufacture of a medicament, especially for the treatment of angiotensin-induced hypertension, of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof.

The invention also provides processes for preparing the compounds of the invention, which are described in more detail hereafter.

In the compounds of the invention, R^1 may represent an alkyl group, a cycloalkyl group, an aryl group or a heterocyclic group.

Where R^1 represents an alkyl group, this may be a straight or branched chain alkyl group which has from 1 to 10, more preferably from 1 to 8, carbon atoms. Examples of such groups include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, hexyl and octyl groups.

Where R^1 represents a cycloalkyl group, this has from 3 to 8, more preferably from 5 to 7, ring carbon atoms and examples of such groups include the cyclopentyl, cyclohexyl and cycloheptyl groups.

Where R^1 represents an aryl group, this is preferably a carbocyclic aryl group which has from 6 to 14, more preferably from 6 to 10, ring carbon atoms and may comprise a single or multiple (fused) ring system. Preferred examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups.

Where R^1 represents a heterocyclic group, this may be a saturated or unsaturated heterocyclic group and may be monocyclic or polycyclic (preferably bicyclic); it has from 4 to 14, preferably from 5 to 10, ring atoms, of which from 1 to 5, more preferably from 1 to 3, are nitrogen and/or oxygen and/or sulphur hetero-atoms. Where the heterocyclic ring is unsaturated, it may be aromatic or non-aromatic. Examples of such heterocyclic groups include the tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, morpholinyl, furyl, thienyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl (e.g. 1,3,4-thiadiazolyl), oxadiazolyl (e.g. 1,3,4-oxadiazolyl), pyridyl, quinolyl, isoquinolyl and indolyl groups.

These groups represented by R^1 may be unsubstituted or may have at least one substituent selected from the following groups:
except where the group represented by R^1 is itself an alkyl group, C_1-C_6, preferably C_1-C_4, alkyl groups, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl groups;
C_6-C_{10} carbocyclic aryl groups, which may be monocyclic or fused polycyclic (preferably bicyclic) groups and which may themselves be substituted as here defined, particularly the phenyl, 1-naphthyl or 2-naphthyl groups;
except where the group represented by R^1 is an alkyl group, aralkyl groups in which the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl, for example the benzyl, phenethyl, 1-naphthylmethyl, 2-

naphthylmethyl and 3-phenylpropyl groups;
the hydroxy group;
C_1-C_6, preferably C_1-C_4, alkoxy groups, for example the methoxy, ethoxy, propoxy, isopropoxy, butoxy or isobutoxy groups;
aralkyloxy groups, in which the aryl part is C_6-C_{10} carbocyclic aryl, more preferably phenyl, and the alkyl part is C_1-C_6 alkyl, more preferably C_1 or C_2 alkyl and most preferably methyl, for example the benzyloxy group;
aryloxy groups, in which the aryl part is C_6-C_{10} carbocyclic aryl, more preferably phenyl, for example the phenoxy group;
halogen atoms, for example the fluorine, chlorine and bromine atoms;
the nitro, cyano and carboxy groups;
alkoxycarbonyl groups, in which the alkoxy part is C_1-C_6, more preferably C_1-C_3, alkoxy, for example the methoxycarbonyl and ethoxycarbonyl groups;
the amino group;
alkylamino groups in which the alkyl part is C_1-C_6, more preferably C_1-C_4, alkyl, for example the methylamino and ethylamino groups;
dialkylamino groups, in which each alkyl part is C_1-C_6, preferably C_1-C_4, more preferably C_1-C_3, alkyl, for example the dimethylamino or diethylamino groups;
acylamino groups, which can be aliphatic carboxylic acylamino groups, preferably having from 1 to 7, more preferably from 1 to 4, carbon atoms or carbocyclic aromatic carboxylic acylamino groups in which the aromatic part is C_6-C_{10} carbocyclic aryl and is more preferably a phenyl group, for example the acetamido and benzamido groups;
the carbamoyl group;
the alkylcarbamoyl and dialkylcarbamoyl groups, in which the or each alkyl part is C_1-C_6, more preferably C_1-C_4 and most preferably C_1-C_3, alkyl, for example the N-methylcarbamoyl, N-ethylcarbamoyl, dimethylcarbamoyl or diethylcarbamoyl groups;
the mercapto group;
C_1-C_6, more preferably C_1-C_4, alkylthio groups, for example the methylthio or ethylthio groups;
arylthio groups in which the aryl part is C_6-C_{10} carbocyclic aryl, more preferably phenyl, for example the phenylthio group;
C_1-C_6, more preferably C_1-C_4, alkylsulphonyl groups, for example the methanesulphonyl or ethanesulphonyl groups;
arylsulphonyl groups in which the aryl part is C_6-C_{10} carbocyclic aryl, more preferably phenyl, for example the benzenesulphonyl group.

Where the group represented by R^1 is substituted, the maximum number of substituents will, of course, depend upon the size of the group to be substituted and the steric effects exerted by the substituents; if the group represented by R^1 is small, for example a lower alkyl group, and the substituent bulky, then steric hindrance may limit the number of potential substituents; at the other extreme, if the substituent is small, the number of substituents may only be limited by the number of available valencies of the atoms in the group represented by R^1. For example, where the substituent is a fluorine or chlorine atom, R^1 could represent a perfluoroalkyl or perchloroalkyl group. However, in general, from 1 to 3 substituents are preferred, although it should be appreciated that more may be appropriate in specific cases, as is well recognized by those skilled in the chemical arts.

R^3 can represent an alkyl, cycloalkyl, aralkyl, aryl, heterocyclic-substituted alkyl or heterocyclic group.

Where R^3 represents an alkyl group, this is a C_1-C_{10} alkyl group, which may be a straight or branched chain group, more preferably having from 1 to 8 carbon atoms. Examples of such groups include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl and octyl groups.

Where R^3 represents a cycloalkyl group, this has from 3 to 8, more preferably from 5 to 7, ring carbon atoms and preferred such groups include the cyclopentyl, cyclohexyl and cycloheptyl groups.

Where R^3 represents an aralkyl group, the alkyl part is a C_1-C_6, more preferably C_1-C_4 and most preferably C_1-C_3, alkyl group (examples being those C_1-C_6 alkyl groups included amongst the examples of alkyl groups which may be represented by R^1) and the aryl part is a C_6-C_{10} carbocyclic aryl group (examples of which are those groups given as examples of aryl groups which may be represented by R^1), preferably a phenyl group. Preferred aralkyl groups are the benzyl, phenethyl and 3-phenylpropyl groups.

Where R^3 represents a carbocyclic aryl group, this has from 6 to 14, preferably from 6 to 10, ring carbon atoms and may be a monocyclic or fused polycyclic (normally bicyclic) group. Preferred examples include the phenyl, 1-naphthyl and 2-naphthyl groups.

Where R^3 represents a heterocyclic group or an alkyl group having a heterocyclic substituent, the heterocyclic group has from 4 to 14, preferably from 5 to 10, more preferably from 5 to 8, ring atoms, of which from 1 to 5, more preferably from 1 to 3, are nitrogen and/or sulphur and/or oxygen hetero-atoms. The heterocyclic group may be saturated, unsaturated or partially saturated, preferably saturated or unsaturated, and may be monocyclic or fused polycyclic (preferably bicyclic). Examples of such groups include the tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, morpholinyl, furyl, thienyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,3,4-oxadiazolyl), thiadiazolyl (e.g. 1,3,4-thiadiazolyl), pyridyl, quinolyl, isoquinolyl and indolyl groups. Where R^3 represents an alkyl group having such a heterocyclic substituent, the alkyl group itself is a C_1-C_6, preferably C_1-C_4 and more preferably C_1-C_3, alkyl group (which may be a straight or branched chain group) and examples of such groups are the C_1-C_6 groups amongst those given as examples of alkyl groups which may be represented by R^1.

The groups defined above for R^3 may be unsubstituted or may have at least one substituent selected from those substituents defined in (a) and/or (b) above and exemplified as substituents on the groups represented by R^1. As with R^1, where any group represented by R^3 is substituted, the number of substituents is only limited by steric considerations, which, of course, vary depending upon the nature of the substituent and the substituted groups and so cannot be defined in general terms. Normally, however, it is convenient, where such groups are substituted, to have from 1 to 3 substituents, but it should be appreciated that this does not, in any sense, represent a practical limit.

The symbol A can represent a direct single bond between the group represented by R^1 and the carbon atom of the group CH-NH at the 3-position of the lactam ring; alternatively, it can represent a methylene group, an ethylene group, a carbonylmethyl (-CO-CH_2-) group, an oxymethyl (-OCH_2-) group or a thiomethyl (-SCH_2-) group. We prefer that A should represent an ethylene group and more particularly prefer that the group represented by R^1-A- should be:

a straight or branched chain alkyl group having from 4 to 9 carbon atoms, for example a butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, octyl, isooctyl or nonyl group;

a 2-cycloalkylethyl group, in which the cycloalkyl part has 5 or 6 ring carbon atoms, for example a 2-cyclopentylethyl or 2-cyclohexylethyl group;

an aralkyl group having a total of from 7 to 12 carbon atoms, for example a benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl or 2-(2-naphthyl)ethyl group;

a phenoxymethyl or phenylthiomethyl group; or

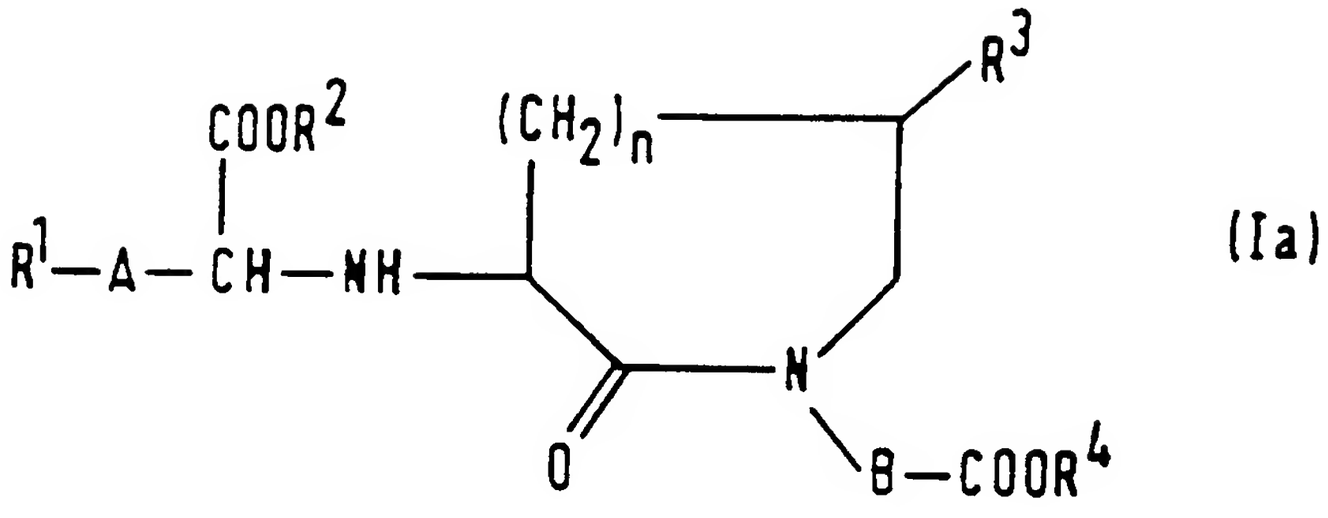
a heterocyclic-substituted ethyl group, for example a 2-(2-thienyl)ethyl, 2-(2-imidazolyl)ethyl or 2(2-thiazolyl)ethyl group.

n may be 1, 2 or 3, but is most preferably 2 or 3.

$\bar{B}$ may represent a C_1-C_4 alkylene group. The two "free" valencies of the alkylene group may be attached to the same carbon atom (in which case the group is sometimes referred to as an "alkylidene" group) or they may be attached to different carbon atoms. Examples of such alkylene groups which may be represented by B are the methylene, ethylene, trimethylene, tetramethylene, ethylidene, propylidene and butylidene groups, preferably the methylene, ethylene and ethylidene groups. B most preferably represents a methylene group.

The compounds of formula (I) have two free carboxy groups and can thus form mono- or di- esters with appropriate ester-forming groups. There is no practical limitation upon the nature of the ester-forming groups employed in this invention, beyond the practical consideration that, if the resulting compounds are in themselves to be used for the treatment of human beings or other animals, the resulting esters must be "pharmaceutically acceptable"; this, as is well known to the skilled man, means that the ester-forming groups must not, or must not to an unacceptable extent, reduce the activity in vivo or increase the toxicity of the compounds. Where the resulting compounds are not in themselves to be used as medicines but, instead, are to be used as intermediates in the preparation of other compounds, even this practical restriction does not apply and any ester appropriate to the intended preparative route may be formed.

The resulting compounds of the invention may be represented by the formula (Ia):



(Ia)

(wherein R^1, R^3, A, B and n are as defined above and R^2 and R^4 are the same or different and each represents a C_1-C_{10} alkyl group, an aralkyl group in which the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or substituted as defined in (c) below and the alkyl part is C_1-C_6 alkyl, a C_6-C_{14} carbocyclic aryl group, a phthalidyl group or a substituted silyl group, e.g. a trialkylsilyl group where each alkyl part is C_1-C_6 alkyl, said groups represented by R^2 and R^4 being unsubstituted or having at least one substituent selected from substituents (c):

substituents (c): C_1-C_6 alkyl groups (except where the parent group is an alkyl group), halogen atoms, hydroxy groups, C_1-C_6 alkoxy groups, (C_1-C_6 alkoxy)-(C_1-C_3 alkoxy) groups, aliphatic and carbocyclic aromatic carboxylic acyloxy groups, oxo groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_6 alkoxy, alkoxycarbonyloxy groups where the alkoxy part is C_1-C_6 alkoxy, aliphatic and carbocyclic aromatic carboxylic acylamino groups, nitro groups, cyano groups, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups where each alkyl part is C_1-C_6 alkyl, C_6-C_{10} carbocyclic arylamino groups, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups, C_6-C_{10} carbocyclic arylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur and/or oxygen hetero-atoms, said heterocyclic groups being unsubstituted or having at least one substituent selected from substituents (a) and (b) above.

Examples of the above substituents have either been given previously in relation to substituents on R^1 or are combinations of substituents exemplified previously.

If desired, the alkyl part of the aralkyl group may be attached to two carbon atoms of the aryl group via two of its carbon atoms to form a partially unsaturated, non-aromatic ring (the unsaturation arising from the carbon atoms of the aryl group) through which this aralkyl group is attached to the remainder of the molecule of the compound of formula (I). Alternatively, the aryl group and the alkyl group may be attached to each other through one carbon atom of each group.

Examples of such groups which may be represented by R^2 and R^4 include:

C_1-C_6 alkyl groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl groups;

aralkyl and diarylalkyl groups, such as the benzyl, benzhydryl (diphenylmethyl), 1-indanyl, 2-indanyl, 1-(1,2,3,4-tetrahydronaphthyl) and 2-(1,2,3,4-tetrahydronaphthyl) groups;

the phthalidyl group;

C_6-C_{10} carbocyclic aryl groups, particularly the phenyl group;

trialkylsilyl groups, particularly the trimethylsilyl and t-butyldimethylsilyl groups; and

such groups listed above having one or more substituents selected from alkyl, halogen, hydroxy, alkoxy, alkoxyalkoxy, acyloxy, oxo, carboxy, alkoxycarbonyl, alkoxycarbonyloxy, acylamino, nitro, cyano, amino, alkylamino, dialkylamino, arylamino, alkylthio, arylthio, alkylsulphonyl, arylsulphonyl and 2-oxo-1,3-dioxolen-4-yl (which may itself be substituted) substituents.

Where substituents are present, their number is only limited by steric considerations, which depend upon the size of the substituent and of the substituted group; however, in general, from 1 to 3 substituents would be present.

Examples of such substituted groups which may be represented by R^2 or R^4 include the 2,2,2-trichloroethyl, 2-iodoethyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, methoxymethyl, 2-methoxyethoxymethyl, p-methoxybenzyl, acetoxymethyl, 1-acetoxyethyl, pivaloyloxymethyl, phenacyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, ethoxycarbonyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, p-nitrobenzyl, 1-cyanoethyl, 2-cyanoethyl, methylthiomethyl, ethylthiomethyl, phenylthiomethyl, 2-methanesulphonylethyl, 2-benzenesulphonylethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl groups.

We particularly prefer that R^2 should represent: a hydrogen atom; a straight or branched chain alkyl

group having from 1 to 6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or hexyl group; an aralkyl group, for example a benzyl group; or a protecting group which allows the protected carboxy group to be converted easily to a free carboxy group in the living body, for example an acetoxymethyl, pivaloyloxymethyl, phthalidyl, 1-(ethoxycarbonyloxy)ethyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

We also particularly prefer that R^4 should represent: a carboxy-protecting group of the type commonly used in organic synthesis, such as a t-butyl, methoxymethyl, 2,2,2-trichloroethyl, benzyl, p-methoxybenzyl or diphenylmethyl group; or a protecting group which allows the protected carboxy group to be converted easily to a free carboxy group in the living body, for example an acetoxymethyl, pivaloyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, phthalidyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

Particularly preferred compounds of the invention are those compounds of formula (Ia) in which:
R^2 and R^4 are the most preferred groups defined above;
R^1-A- represents a straight or branched chain alkyl group having from 4 to 9 carbon atoms, for example a butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, isooctyl, octyl or nonyl group; a cycloalkylethyl group in which the cycloalkyl part has 5 or 6 ring carbon atoms, for example a 2-cyclopentylethyl or 2-cyclohexylethyl group; an aralkyl group having a total of from 7 to 12 carbon atoms, for example a benzyl, phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-(1-naphthyl)ethyl or 2-(2-naphthyl)ethyl group; a phenoxymethyl group; a phenylthiomethyl group; a 2-(2-thienyl)ethyl group; a 2-(2-imidazolyl)ethyl group; or a 2-(2-thiazolyl)ethyl group;
R^3 represents a straight or branched chain alkyl group having from 1 to 6 carbon atoms, for example a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl or hexyl group; a cycloalkyl group having 5 or 6 ring carbon atoms, e.g. a cyclopentyl or cyclohexyl group; an aralkyl group having a total of from 7 to 11 carbon atoms, such as a benzyl or 1-naphthylmethyl group; an aryl group, such as a phenyl, p-fluorophenyl, 1-naphthyl or 2-naphthyl group; a heterocyclylmethyl group, such as a 2-imidazolylmethyl or 2-indolylmethyl group; or a heterocyclic group, such as a 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-thiazolyl, 2-pyridyl or 3-pyridyl group;
B represents a methylene group; and
n is 2 or 3.

Still more preferred compounds are those in which:
R^1 represents a C_4-C_7 alkyl group, a C_5 or C_6 cycloalkyl group, a phenyl group or a phenyl group having at least one substituent selected from substituents (a) and (b) defined above;
R^2 represents a hydrogen atom, a C_1-C_4 alkyl group or a benzyl group;
R^3 represents a C_3-C_6 alkyl group, a phenyl group or a phenyl group having at least one substituent selected from substituents (a) and (b) defined above;
R^4 represents a hydrogen atom, a C_1-C_4 alkyl group, a benzyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents a C_1 or C_2 alkylene group;
B represents a methylene group; and
n is 2.

The most preferred compounds are those in which:
R^1 represents a butyl, pentyl, hexyl, cyclohexyl or phenyl group;
R^2 represents a hydrogen atom, a C_2-C_4 alkyl group, particularly an ethyl or butyl group, or a benzyl group;
R^3 represents a phenyl group or a halophenyl group;
R^4 represents a hydrogen atom, a C_2-C_4 alkyl group, particularly a t-butyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents an ethylene group;
B represents a methylene group; and
n is 2.

Where the compounds of the invention contain one or two free carboxy groups, these compounds may also form salts with bases; the nature of the cation of the resulting salt is not critical to the present invention and, where the resulting compounds are for use as medicines, is only limited to the extent that the resulting salt must be pharmaceutically acceptable; where the compound is subsequently to be used as an intermediate for the production of another compound, even this restriction is not applicable. Of course, there are practical constraints, such as cost and availability of the bases used to form the salts, but these constraints vary from time to time and are irrelevant to the essence of the present invention. Examples of suitable salts include: alkali metal salts, for example sodium or potassium salts; alkaline earth metal salts, for example calcium or magnesium salts; other metal salts, for example aluminium salts; ammonium salts; salts with organic bases, for example triethylamine, dicyclohexylamine, cinchonine, guanidine or quinine

salts; and salts with basic amino acids, for example lysine or arginine salts.

The compounds of the invention also contain an amino group which can potentially exert a basic effect and the compounds can thus also form acid addition salts. Where the compounds are to be used as medicines, the nature of such salts is only limited to the extent that the resulting compound should be pharmaceutically acceptable; where the compound is to be used as an intermediate, this criterion does not apply and any acid may be employed. Examples of suitable acids include inorganic acids, such as hydrogen halides, (for example hydrochloric acid or hydrobromic acid), sulphuric acid, phosphoric acid or nitric acid; organic carboxylic acids, for example oxalic acid, maleic acid, fumaric acid, tartaric acid or citric acid; and organic sulphonic acids, such as methanesulphonic acid or benzenesulphonic acid.

Specific examples of compounds of the invention are given in the following Table in which the definitions given relate to the foregoing formula (Ia). In this Table, the following abbreviations are employed:

Bu	butyl
iBu	isobutyl
$\bar{t}$Bu	t-butyl
$\bar{B}$z	benzyl
Dom	(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
Et	ethyl
Etc	ethoxycarbonyl
Ety	ethylene (-CH_2CH_2-)
Fur	furyl
cHx	cyclohexyl
$\bar{M}$e	methyl
Np	naphthyl
Oc	octyl
Ph	phenyl
Piv	pivaloyl
iPr	isopropyl
$\bar{T}$hi	thienyl

Table

Cpd No.	R^1-A	R^2	R^3	R^4	B	n
1	2-PhEt	H	Ph	H	CH_2	2
2	2-PhEt	Et	Ph	H	CH_2	2
3	2-PhEt	Bu	Ph	H	CH_2	2
4	2-PhEt	Bz	Ph	H	CH_2	2
5	2-PhEt	Et	Ph	tBu	CH_2	2
6	2-PhEt	Et	Ph	Bz	CH_2	2
7	2-PhEt	H	Me	H	CH_2	2
8	2-PhEt	Et	Me	H	CH_2	2
9	2-PhEt	Bu	Me	H	CH_2	2
10	2-PhEt	Bz	Me	H	CH_2	2
11	2-PhEt	Et	Me	tBu	CH_2	2
12	2-PhEt	H	iPr	H	CH_2	2
13	2-PhEt	Et	iPr	H	CH_2	2
14	2-PhEt	Bu	iPr	H	CH_2	2
15	2-PhEt	Bz	iPr	H	CH_2	2
16	2-PhEt	Et	iPr	tBu	CH_2	2
17	2-PhEt	H	2-Thi	H	CH_2	2
18	2-PhEt	Et	2-Thi	H	CH_2	2
19	2-PhEt	Bu	2-Thi	H	CH_2	2

Table (cont)

Cpd No.	R^1-A	R^2	R^3	R^4	B	n
20	2-PhEt	Bz	2-Thi	H	CH_2	2
21	2-PhEt	Et	2-Thi	tBu	CH_2	2
22	2-PhEt	H	3-Thi	H	CH_2	2
23	2-PhEt	Et	3-Thi	H	CH_2	2
24	2-PhEt	Bu	3-Thi	H	CH_2	2
25	2-PhEt	Bz	3-Thi	H	CH_2	2
26	2-PhEt	Et	3-Thi	tBu	CH_2	2
27	2-PhEt	H	2-Fur	H	CH_2	2
28	2-PhEt	Et	2-Fur	H	CH_2	2
29	2-PhEt	Bu	2-Fur	H	CH_2	2
30	2-PhEt	Bz	2-Fur	H	CH_2	2
31	2-PhEt	Et	2-Fur	tBu	CH_2	2
32	2-PhEt	H	Bz	H	CH_2	2
33	2-PhEt	Et	Bz	H	CH_2	2
34	2-PhEt	Bu	Bz	H	CH_2	2
35	2-PhEt	Bz	Bz	H	CH_2	2
36	2-PhEt	Et	Bz	tBu	CH_2	2
37	2-PhEt	H	cHx	H	CH_2	2
38	2-PhEt	Et	cHx	H	CH_2	2
39	2-PhEt	Bu	cHx	H	CH_2	2
40	2-PhEt	Bz	cHx	H	CH_2	2
41	2-PhEt	Et	cHx	tBu	CH_2	2
42	2-cHxEt	H	Ph	H	CH_2	2

Table (cont)

Cpd No.	R^1-A	R^2	R^3	R^4	B	n
43	2-cHxEt	Et	Ph	H	CH_2	2
44	2-cHxEt	Bu	Ph	H	CH_2	2
45	2-cHxEt	Bz	Ph	H	CH_2	2
46	2-cHxEt	Et	Ph	tBu	CH_2	2
47	Oc	H	Ph	H	CH_2	2
48	Oc	Et	Ph	H	CH_2	2
49	Oc	Bu	Ph	H	CH_2	2
50	Oc	Bz	Ph	H	CH_2	2
51	Oc	Et	Ph	tBu	CH_2	2
52	iBu	H	Ph	H	CH_2	2
53	iBu	Et	Ph	H	CH_2	2
54	iBu	Bu	Ph	H	CH_2	2
55	iBu	Bz	Ph	H	CH_2	2
56	iBu	Et	Ph	Bz	CH_2	2
57	2-cHxEt	H	2-Thi	H	CH_2	2
58	2-cHxEt	Et	2-Thi	H	CH_2	2
59	Oc	H	2-Thi	H	CH_2	2
60	Oc	Et	2-Thi	H	CH_2	2
61	iBu	H	2-Thi	H	CH_2	2
62	iBu	Et	2-Thi	H	CH_2	2
63	2-PhEt	H	Ph	H	>CHMe	2
64	2-PhEt	Et	Ph	H	>CHMe	2
65	2-PhEt	H	Ph	H	Ety	2

Table (cont)

Cpd No.	R^1-A	R^2	R^3	R^4	B	n
66	2-PhEt	Et	Ph	H	Ety	2
67	2-PhEt	H	Ph	H	CH_2	3
68	2-PhEt	Et	Ph	H	CH_2	3
69	2-PhEt	Bu	Ph	H	CH_2	3
70	2-PhEt	Bz	Ph	H	CH_2	3
71	2-PhEt	Et	Ph	tBu	CH_2	3
72	2-PhEt	H	2-Thi	H	CH_2	3
73	2-PhEt	Et	2-Thi	H	CH_2	3
74	2-PhEt	Bu	2-Thi	H	CH_2	3
75	2-PhEt	Bz	2-Thi	H	CH_2	3
76	2-PhEt	Et	2-Thi	tBu	CH_2	3
77	2-PhEt	H	Ph	H	CH_2	1
78	2-PhEt	Et	Ph	H	CH_2	1
79	2-PhEt	H	2-Thi	H	CH_2	1
80	2-PhEt	Et	2-Thi	H	CH_2	1
81	2-PhEt	Et	Ph	PivOMe	CH_2	2
82	2-PhEt	Et	Ph	1-(EtcO)Et	CH_2	2
83	2-PhEt	Et	Ph	Dom	CH_2	2
84	2-PhEt	H	4-FcHx	H	CH_2	2
85	2-PhEt	Et	4-FcHx	H	CH_2	2
86	2-PhEt	Bu	4-FcHx	H	CH_2	2

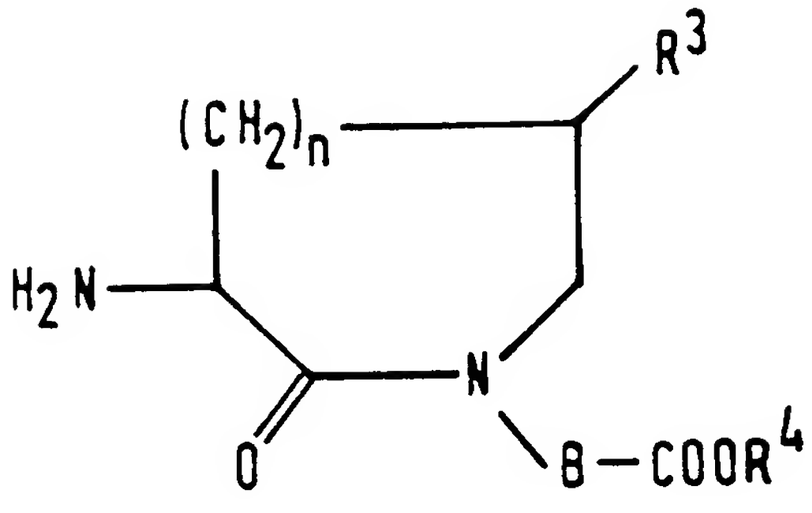
Table (cont)

Cpd No.	R^1-A	R^2	R^3	R^4	B	n
87	2-PhEt	Bz	4-F<u>c</u>Hx	H	CH_2	2
88	2-PhEt	H	1-Np	H	CH_2	2
89	2-PhEt	Et	1-Np	H	CH_2	2
90	2-PhEt	Bu	1-Np	H	CH_2	2
91	2-PhEt	Bz	1-Np	H	CH_2	2
92	2-PhEt	H	2-Np	H	CH_2	2
93	2-PhEt	Et	2-Np	H	CH_2	2
94	2-PhEt	Bu	2-Np	H	CH_2	2
95	2-PhEt	Bz	2-Np	H	CH_2	2
96	2-PhEt	Et	<u>p</u>-FPh	<u>t</u>Bu	CH_2	2
97	2-PhEt	Bu	<u>p</u>-FPh	<u>t</u>Bu	CH_2	2
98	2-PhEt	Bu	Ph	<u>t</u>Bu	CH_2	2

Of the compounds listed above, preferred compounds from the point of view of their biological activity, are Compounds Nos. 1, 2, 3, 5, 84, 85, 86, 96, 97 and 98, Compounds Nos. 1, 2, 3, 84, 85 and 86 being most preferred.

The compounds of the present invention can contain many asymmetric carbon atoms and can thus exist in the form of many stereoisomers and the present invention envisages both the individual isolated isomers as well as mixtures thereof. The following carbon atoms are asymmetric in all of the compounds of the invention: the carbon atom to which the group represented by R^1-A- is attached; the carbon atom at the 3-position of the lactam ring; and the carbon atom to which the group represented by R^3 is attached. In addition, depending upon the nature of the substituent groups on the compounds of the invention, other carbon atoms may also be asymmetric. The compounds of the invention may be prepared as mixtures of isomers and then separated by conventional techniques or they may be prepared by stereo-specific synthesis techniques, all of which are well-known to those skilled in the art.

The compounds of the present invention can be prepared by the condensation of a compound of formula (II):



(II)

(in which R^3, R^4, B and n are as defined above) with a compound of formula (IIIa):

R^1-A-C(=Y)-COOR^2 (IIIa)

(in which R^1, R^2 and A are as defined above and Y represents either one hydrogen atom plus one halogen atom or one sulphonyloxy group or, where the condensation is carried out under reductive conditions, a single oxygen atom), i.e. a compound of formula (III):

R^1-A-CH(COOR^2)-X (III)

(in which R^1, R^2 and A are as defined above and x represents a halogen atom or a sulphonyloxy group) or by reductive condensation of the aforementioned compound of formula (II) with a compound of formula (IV):

R^1-A-C(=O)-COOR^2 (IV)

(in which R^1, R^2 and A are as defined above).

In the compound of formula (III), where X represents a halogen atom, this is preferably a chlorine, bromine or iodine atom; where X represents a sulphonyloxy group, this is preferably a substituted or unsubstituted C_1-C_6 alkanesulphonyloxy group, such as a methanesulphonyloxy, ethanesulphonyloxy or trifluoromethanesulphonyloxy group, or a substituted or unsubstituted aromatic sulphonyloxy group, such as a benzenesulphonyloxy, p-toluenesulphonyloxy, p-nitrobenzenesulphonyloxy, o-nitrobenzenesulphonyloxy, m-nitrobenzenesulphonyloxy, 2,4-dinitrobenzenesulphonyloxy, 4-chloro-3-nitrobenzenesulphonyloxy, p-bromobenzenesulphonyloxy, p-chlorobenzenesulphonyloxy or 2,5-dichlorobenzenesulphonyloxy group; in the case of the substituted groups, substituents are selected from substituents (a) and (b) defined above.

Condensation of the compound of formula (II) with the compound of formula (III) is preferably effected in the presence of a solvent and of a base. The nature of the solvent is not critical, provided that it has no adverse effect upon the reaction; suitable solvents include: aliphatic and aromatic hydrocarbons, such as hexane or benzene; halogenated aliphatic or aromatic, preferably aliphatic, hydrocarbons, such as methylene chloride or 1,2-dichloroethane; ethers, such as tetrahydrofuran or dioxane; esters, such as ethyl acetate; ketones, such as acetone; amides, such as dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone or hexamethylphosphoric triamide; sulphoxides, such as dimethyl sulphoxide; and nitriles, such as acetonitrile. There is likewise no criticality as to the nature of the base to be employed, provided that it does not adversely affect the reaction. Suitable bases include, for example: alkali metal and alkaline earth metal carbonates, such as sodium carbonate, potassium carbonate or calcium carbonate; alkali metal bicarbonates, such as sodium bicarbonate or potassium bicarbonate; alkali metal hydrides, such as sodium hydride or lithium hydride; metal fluorides, such as potassium fluoride or cesium fluoride; and organic bases, such as triethylamine, pyridine, picoline or tetraethylammonium hydroxide. If desired, the reaction may be carried out in a two-phase reaction system employing water as the solvent for one phase and a water-immiscible solvent (such as methylene chloride or chloroform) for the other phase; in this case, a phase-transfer catalyst (such as tetrabutylammonium bromide or benzyltriethylammonium iodide) should be employed and the base may be a relatively strong base, such as an alkali metal hydroxide (for example sodium hydroxide or potassium hydroxide).

The reaction will take place over a wide range of temperatures and the precise temperature chosen is not critical to the present invention; we generally find it convenient to carry out the reaction at a temperature within the range from 0 to 120°C. The time required for the reaction will vary depending upon many

factors, but primarily upon the natures of the solvent, base and reagents, and upon the reaction temperature, but a period of from 1 hour to 5 days will normally suffice.

After completion of the reaction, the desired compound may be obtained from the reaction mixture by conventional means. For example, one suitable recovery technique comprises: adding an organic solvent, such as ethyl acetate, to the reaction mixture; separating the organic layer and washing it with water; drying the organic layer; and distilling off the solvent to give the desired product. If necessary, this product can be further purified by various conventional techniques, such as recrystallization and/or the chromatography techniques, particularly column chromatography.

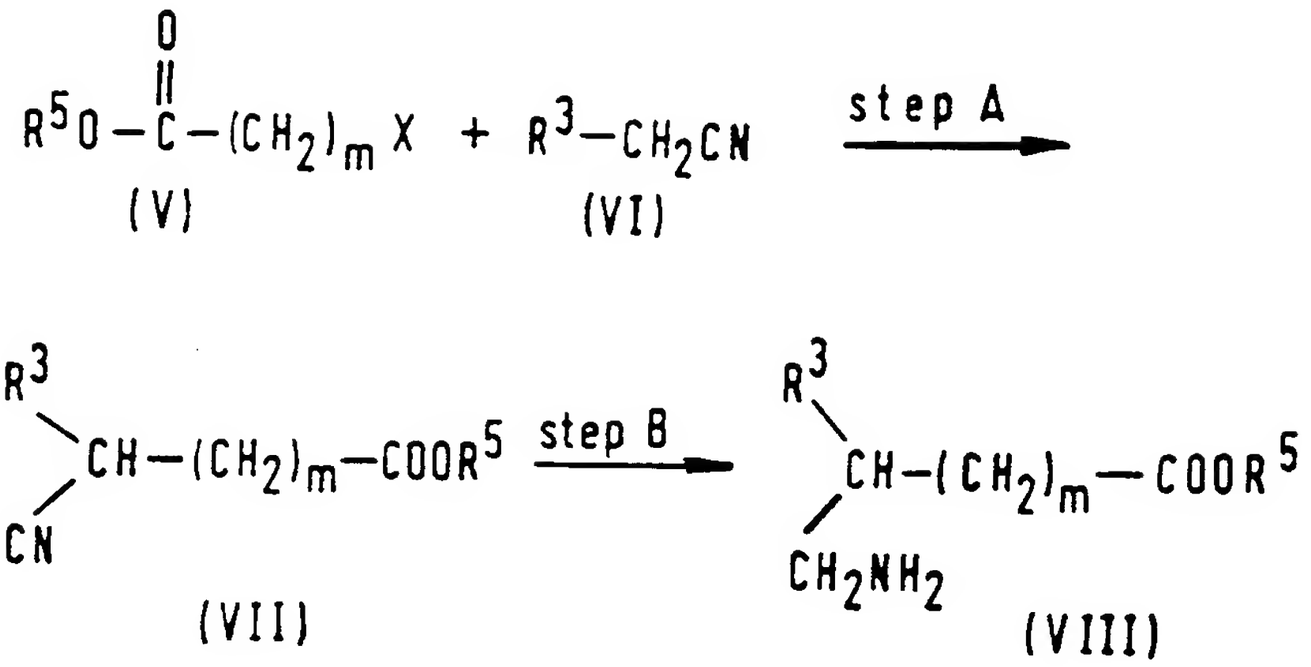
Reaction of the compound of formula (II) with the compound of formula (IV) takes place under reductive condensation conditions. The reductive conditions may be provided by a variety of means, for example: catalytic reduction using a metal, such as platinum, palladium, Raney nickel or rhodium, optionally on a carrier, in the presence of hydrogen; reduction with a metal hydride, such as lithium aluminium hydride, lithium borohydride, lithium cyanoborohydride, sodium cyanoborohydride, sodium borohydride or potassium borohydride; reduction with an active metal, such as sodium or magnesium, together with an alcohol, such as methanol or ethanol; or reduction with a metal, such as iron or zinc, and an acid, such as hydrochloric acid or acetic acid. The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon (although it may participate in) the reaction. Suitable solvents include water and a variety of organic solvents, for example: alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran, diethyl ether or dioxane; halogenated hydrocarbons, particularly halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; esters, such as ethyl acetate; aromatic hydrocarbons, such as benzene or toluene; amides, such as dimethylformamide or dimethylacetamide; and organic carboxylic acids, such as acetic acid. It will be noted that certain of the compounds mentioned herein as potential solvents may also serve as part of the reduction system described above and, in that case, the same compound may serve both as a reagent and as a solvent, if desired.

The reaction will take place over a wide range of temperatures, for example from -20 °C to +100 °C, although the precise temperature chosen will depend upon several factors, of which the most important is the nature of the reductive system employed. The reaction can be carried out under atmospheric pressure, although, in some cases, it may be desirable to carry it out under an elevated or reduced pressure.

Of the compounds of formula (I), the monoester monocarboxylic acids in which R^2 represents an ester residue and R^4 represents a hydrogen atom and the dicarboxylic acids in which both R^2 and R^4 represent hydrogen atoms, as well as the salts of these acids, are medically the most important compounds. The monoester monocarboxylic acid can be prepared by selective deprotection of the ester residue represented by R^4 in a diester compound in which both R^2 and R^4 represent ester residues: alternatively, it may be prepared by the reductive condensation of an amino acid of formula (II) in which R^4 represents a hydrogen atom with a ketoester of formula (IV) in which R^2 represents an ester residue.

A dicarboxylic acid of formula (I) in which both R^2 and R^4 represent hydrogen atoms can also be prepared by hydrolyzing a diester or monoester of formula (I) (in which R^2 and R^4 represent ester residues or R^2 represents an ester residue and R^4 represents a hydrogen atom) with an acid or base: it may also be prepared by reductive removal of the ester group or groups of the diester or monoester, or (when the compound contains an allyl ester group) catalytic removal of the allyl group with a suitable catalyst such as tetrakis(triphenylphosphine)palladium (O). The reaction conditions employed are the same as those described for deprotection of the carboxy-protecting group represented by R^5 in the compound of formula (V) described hereafter.

The starting materials of formula (II) employed in the processes of the present invention may be prepared in a variety of ways, for example, by the process illustrated in the following reaction scheme:



In the above formulae, R^3, R^4, B and n are as defined above. m = (n + 1) and R^5 represents a carboxy-protecting group.

The nature of the carboxy-protecting group represented by R^5 is not critical to the present invention, as its purpose is merely to protect the carboxy group from participation in the reaction of Steps A and B and it is then immediately eliminated in Step C. Accordingly, any protecting group known in the art for use in this

type of reaction may be employed, normally an ester residue. Examples include: methyl and substituted methyl groups, such as the methyl, allyl, methoxymethyl, methylthiomethyl, 2-methoxyethoxymethyl, benzyloxymethyl, phenacyl, p-bromophenacyl or phthalimidomethyl groups; other lower (e.g. C_2-C_6, preferably C_2-C_4) alkyl groups, which may be substituted or unsubstituted, for example the ethyl, 2,2,2-trichloroethyl, 2-iodoethyl, 2-trimethylsilylethyl, 2-(p-toluenesulphonyl)ethyl or t-butyl groups; benzyl groups which may be substituted or unsubstituted, for example the benzyl, benzhydryl (i.e. diphenylmethyl), p-methoxybenzyl or p-nitrobenzyl groups; or silyl groups, preferably trialkylsilyl groups in which each alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, for example the trimethylsilyl or t-butyldimethylsilyl groups. It should, however, be appreciated that these groups are given merely by way of exemplification and there is no limitation on the nature of the carboxy-protecting group, provided that it is capable of serving a protecting function.

In Step A of the reaction scheme, the acetonitrile derivative of formula (VI) is C-alkylated with the protected carboxyalkyl halide of formula (V). This reaction is preferably effected in the presence of a base and in a suitable solvent. The nature of the solvent employed is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: hydrocarbons, which may be aliphatic, cycloaliphatic or aromatic, such as hexane or benzene; halogenated hydrocarbons, particularly halogenated aliphatic hydrocarbons, such as methylene chloride; ethers, such as tetrahydrofuran or dioxane; esters, such as ethyl acetate; and amides, such as dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone and hexamethylphosphoric triamide. There is likewise no criticality as to the nature of the base employed, provided that it does not interfere with the reaction. Suitable bases include: alkali metal hydrides, such as sodium hydride, lithium hydride or potassium hydride; alkyl-alkali metal compounds, such as butyllithium; alkali metal amides, such as lithium diisopropylamide, lithium dicyclohexylamide or lithium bis-(trimethylsilyl)amide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and organic amines, such as triethylamine, triethylenediamine, 1,5-diazabicyclo[4.3.0]nonene-5 or 1,8-diazabicyclo[5.4.0]undecene-7. If desired, the reaction may be carried out in a two-phase reaction system, employing water as the solvent for one phase and a water-immiscible solvent (such as methylene chloride or chloroform) for the other phase; in this case, a phase-transfer catalyst (such as tetrabutylammonium bromide or benzyltriethylammonium iodide) should be employed, and the base may be a relatively strong base, such as an alkali metal hydroxide (for example sodium hydroxide or potassium hydroxide).

The reaction will take place over a wide range of temperatures and the precise temperature chosen is not critical to the present invention. In general, we find it convenient to carry out the reaction at a temperature within the range from -20 °C to +100 °C. The time required for the reaction may vary widely, depending upon many factors, but notably upon the reaction temperature; at temperatures within the range suggested, a period of from 30 minutes to 24 hours will normally suffice.

After completion of the reaction, the desired compound may be recovered from the reaction mixture by conventional means. For example, one suitable recovery technique comprises: adding an organic solvent, such as ethyl acetate, to the reaction mixture; separating the organic layer and washing it with water; drying the organic layer; and distilling off the solvent to give the desired product. If necessary, this product can be further purified by various conventional techniques, such as recrystallization and/or the various chromatography techniques, notably column chromatography.

In Step B, the nitrile compound of formula (VII) is reduced to the corresponding aminomethyl compound of formula (VIII). This reaction may be carried out under similar conditions and employing similar reagents to those described in relation to the reductive condensation of the compound of formula (II) with the compound of formula (IV). After the reduction, the product of formula (VIII) can be purified by various known means, for example by recrystallization, the various chromatography techniques, such as column chromatography, or salt formation with an organic or inorganic acid.

In Step C, the carboxy-protecting group represented by R^5 is removed by conventional means well-known to those skilled in chemical synthesis and the particular reaction employed to remove this group is not critical to the present process. The precise removal reaction chosen will, of course, depend upon the precise nature of the carboxy-protecting group represented by R^5, for example:

where R^5 represents an alkyl group, such as a methyl or ethyl group, the compound may be deprotected by hydrolysis with an alkali, preferably an alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide or potassium hydroxide;

where R^5 represents a protecting group such as a methoxymethyl, methoxyethoxymethyl, t-butyl, benzhydryl, p-methoxybenzyl, trimethylsilyl or t-butyldimethylsilyl group, the compound may be deprotected by reaction with an acid or a Lewis acid, such as hydrochloric acid, hydrobromic acid, trifluoroacetic acid or aluminium chloride;

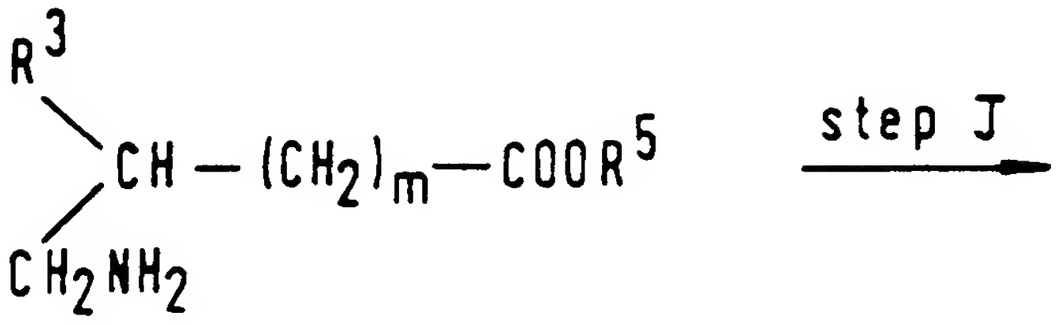
where R^5 represents a group such as a benzyl or p-nitrobenzyl group, the compound may be deprotected

by catalytic reduction, employing hydrogen in the presence of a suitable catalyst, for example palladium, which may be supported, for example, on carbon;
where R^5 represents a group such as a 2,2,2-trichloroethyl, 2-iodoethyl, phenacyl or p-bromophenacyl group, the compound may be deprotected by reduction employing a mixture of a metal powder (e.g. zinc powder) and an acid (e.g. acetic acid or hydrochloric acid); or
where R^5 represents a group such as an allyl group, the compound may be deprotected by a catalytic reaction, employing, for example, tetrakis(triphenylphosphine)palladium (O).

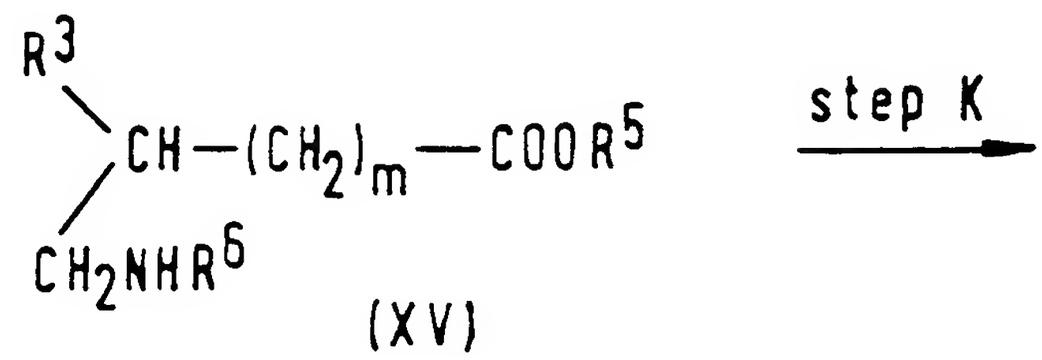
The reaction in this deprotection Step C is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. The optimum solvent will, of course, depend upon the precise reaction chosen and as is obvious to those skilled in the art, in some cases, the solvent may participate in the deprotection reaction. In general terms, suitable solvents may be chosen from the class consisting of: water; acids, preferably organic carboxylic and more preferably aliphatic carboxylic, acids such as acetic acid or formic acid; alcohols, such as methanol or ethanol: ethers, such as tetrahydrofuran, dioxane or anisole; ketones, such as acetone; halogenated hydrocarbons, preferably halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; and hydrocarbons, which may be aliphatic or aromatic, preferably aromatic, such as benzene or toluene. These reactions will take place over a wide range of temperatures, for example at a temperature within the range from -10 °C to +100 °C; in general, the time allowed for the reaction will vary depending upon the nature of the deprotection reaction and other reaction conditions, including the reaction temperature; at one extreme, a relatively fast reaction will be complete within perhaps 30 minutes, whereas, at the other extreme, it may be advisable to allow 24 hours for the reaction: however, these are matters well within the skill and knowledge of the laboratory technician.

If desired, the compound of formula (IX) may be purified by various conventional means, for example by isoelectric precipitation, recrystallization or the various chromatography techniques, such as column chromatography.

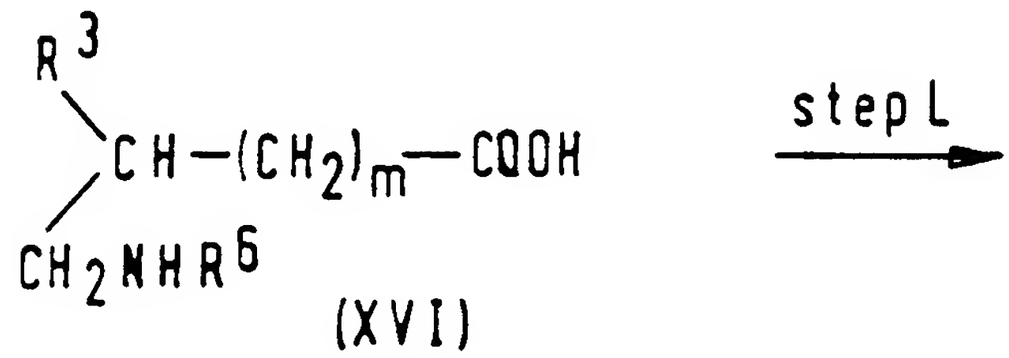
However, if purification of the compound of formula (IV) is troublesome, the amino acid compound of formula (IX) can be prepared by the alternative reaction sequence shown below:



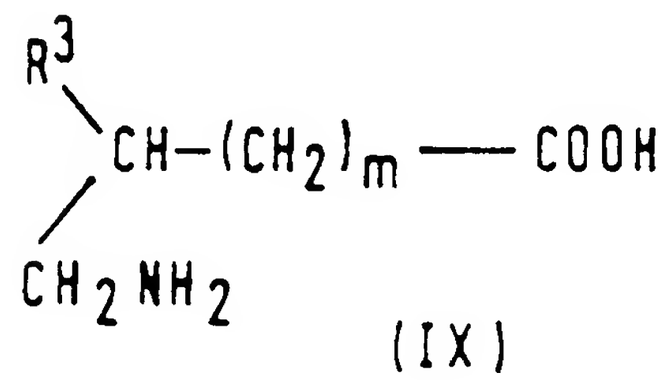
(VIII)



(XV)



(XVI)



(IX)

In these formulae, R^3, R^5 and m are as defined above and R^6 represents an amino-protecting group. There is no criticality as to the nature of the amino-protecting group represented by R^6 as this group is removed in the course of the reaction and thus does not appear in the final product. Accordingly, it has no influence on the nature of the final product and may be chosen having regard solely to its protecting function. Examples of such protecting groups include: alkoxycarbonyl groups, in which the alkoxy part preferably has from 1 to 6, more preferably from 1 to 4, carbon atoms and which may be substituted or unsubstituted [examples of substituents being any of those groups and atoms listed above as substituents (a) and (b) as well as lower (e.g. C_1-C_4) alkylidene groups], for example the 2,2,2-trichloroethoxycarbonyl, 2-iodoethoxycarbonyl, 2-(p-toluenesulphonyl)ethoxycarbonyl, trimethylsilylethoxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl, p-methoxybenzyloxycarbonyl or p-nitrobenzyloxycarbonyl groups; C_1-C_7 aliphatic carboxylic acyl or (C_6-C_{10} carbocyclic aryl) carboxylic acyl groups, which may be unsubstituted or have one or more of the substituents listed in groups (a) and (b) above, for example the formyl, acetyl, benzoyl, chloroacetyl or trifluoroacetyl groups; cyclic diacyl groups, such as the phthaloyl or 2,3-diphenylmalonyl groups; substituted methyl groups, such as the methoxymethyl, benzyloxymethyl, benzyl, 3,4-dimethoxybenzyl or trityl groups; alkylidene or aralkylidene groups, such as the isopropylidene, benzylidene or salicylidene groups; acylvinyl groups, such as the 2-acetyl-1-methylvinyl or 2-benzoyl-1-methylvinyl groups; and silyl groups, particularly trialkylsilyl groups in which each alkyl part has from 1 to 6, preferably from 1 to 4, carbon atoms, for example the trimethylsilyl or t-butyldimethylsilyl groups. It should, however, be appreciated that these groups are given by way of example only and that the nature of the group is not critical, provided that it serves its required protecting function.

In Step J of this route, the amino group in the compound of formula (VIII) is first protected by conventional means to give the compound of formula (XV). Then, in Step K, the carboxy-protecting group represented by R^5 is removed by the appropriate one of the reactions described above. Finally, in Step L, the amino-protecting group represented by R^6 is removed by conventional means to prepare the amino acid compound of formula (IX). This route is particularly advantageous if the compound of formula (XV) crystallizes easily and so may be purified without difficulty.

In Step D, the compound of formula (IX) is cyclized to form a corresponding lactam of formula (X) by condensing the free amino group with the free carboxy group, to form an amide linkage, of a type which is well-known in the field of peptide chemistry. This reaction may generally be carried out by contacting the compound of formula (IX) with a dehydrating agent, such as N,N'-dicyclohexylcarbodiimide, carbonyldiimidazole, diphenylphosphoryl azide, diethyl cyanophosphate or phosphorus pentachloride. If a dehydrating agent of the carbodiimide type is employed, the reaction can be accelerated by carrying out the reaction in the presence of 1-hydroxybenzotriazole, N-hydroxysuccinimide or a similar compound. It may also be advantageous to carry out the reaction in the presence of a base, which may be an organic base, for example pyridine, picoline, triethylamine or N-methylmorpholine, or an inorganic base, such as sodium carbonate or sodium bicarbonate. The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: amides, such as dimethylformamide, hexamethylphosphoric triamide, N-methyl-2-pyrrolidone or dimethylacetamide; ethers, such as tetrahydrofuran or dioxane; nitriles, such as acetonitrile; lower alcohols, such as methanol or ethanol; ketones, such as acetone; halogenated hydrocarbons, preferably aliphatic hydrocarbons, such as methylene chloride or chloroform; esters, such as ethyl acetate; or aromatic hydrocarbons, such as benzene or toluene. Sometimes, the product can be isolated as crystals from the reaction mixture; at other times, other recovery techniques (such as those described elsewhere in the specification) may be employed; if desired, the product can be purified by various conventional techniques, such as the chromatography techniques, especially column chromatography.

In Step E, the compound of formula (X) is brominated, to introduce a bromine atom at the 3-position of the lactam derivative (X). This may, for example, be carried out using phosphorus pentachloride and bromine according to the method reported by Nagasawa et al [Journal of Medicinal Chemistry 14. 501 (1971)].

In Step F, the resulting compound of formula (XI) is reacted with an azide to convert the bromine atom to an azido group in the compound of formula (XII). The azide is preferably an alkali metal azide, such as sodium azide or lithium azide. The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: amides, such as dimethylformamide, dimethylacetamide or N-methyl-2-pyrrolidone; ethers, such as tetrahydrofuran or dioxane; ketones, such as acetone; and nitriles, such as acetonitrile. The reaction will take place over a wide range of temperatures and the precise temperature chosen is not critical to the reaction. We generally find it convenient to carry out the reaction at a temperature in the range from room temperature to 100°C. The time required for the reaction may vary widely, depending upon many factors, notably the reaction temperature; however, at the temperatures suggested above, a period of from 1 to 24 hours will normally suffice. The desired compound of formula (XII) can then be obtained from the reaction system by, for example, extracting it with a solvent (such as ethyl acetate), washing the extract with water and then distilling off the organic solvent. If necessary, the product can be purified by conventional means, particularly the various chromatography techniques, such as column chromatography.

In Step G of the reaction scheme, the compound of formula (XIV) can be prepared by N-alkylation of the compound of formula (XII), employing a compound of formula (XIII):

$$X\text{-}B\text{-}COOR^4 \qquad (XIII)$$

[in which B and R^4 are as defined above and X represents a halogen atom or a sulphonyloxy group, examples of which are given in relation to the atom or group represented by X in the compound of formula (III), preferably a bromine atom]. The reaction may be effected under the same conditions and employing the same reagents as described above in relation to Step A. The desired compound of formula (XIV) may be recovered from the reaction mixture by conventional means. For example, one suitable recovery technique comprises: adding an organic solvent, such as ethyl acetate, to the reaction mixture; separating the organic layer and washing it with water; drying the organic layer; and then finally distilling off the solvent to give the desired compound. If necessary, this compound may be further purified by such conventional means as the various chromatography techniques, particularly column chromatography.

In Step H, the azido group is reduced to an amino group by any method well-known in the field of

organic synthesis. Examples of suitable reactions include:
catalytic reduction in the presence of hydrogen, using, as catalyst, a metal, such as palladium, platinum or Raney nickel, on a suitable catalyst, for example carbon in an appropriate form;
reduction with a metal hydride, such as sodium borohydride; or
reduction by reaction with a thiol, such as 1,3-propanedithiol.

The reduction reaction is normally effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol or ethanol; ethers, such as tetrahydrofuran, diethyl ether or dioxane; halogenated hydrocarbons, particularly halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; esters, such as ethyl acetate; hydrocarbons, particularly aromatic hydrocarbons, such as benzene or toluene; amides, such as dimethylformamide or dimethylacetamide; lower fatty acids, such as acetic acid; and water. The reaction will take place over a wide range of temperatures and the particular temperature chosen is not critical. We generally find it convenient to carry out the reaction at a temperature in the range from -20°C to +100°C. After completion of the reaction, the product may, if required, be further purified by conventional techniques, such as column chromatography or salt formation with an organic or inorganic acid.

In the compounds of formulae (II), (XII) and (XIV), the carbon atom to which the amino group or the azido group is attached and the carbon atom to which the group represented by R^3 is attached are both asymmetric carbon atoms. Hence, two kinds of isomers can exist in the racemate of each of these compounds: one isomer in which the amino or azido group and R^3 are in the same orientation (the cis configuration); and the other isomer in which these groups are in the opposite orientation (the trans configuration). If necessary, these diasteromers may be separated by chromatography or fractional recrystallization. Furthermore, when such compounds containing amino or carboxy groups as the compounds of formulae (II), (VIII) and (IX) are racemic, the mixture of optical isomers may be separated by conventional resolution methods, for example the formation of salts with optically active bases, such as cinchonine, cinchonidine, quinine or quinidine, or with optically active organic acids, e.g. l-camphorsulphonic acid or d-camphorsulphonic acid. Optical isomers can also be resolved by other known techniques, including various kinds of chromatography, fractional crystallization etc.

As noted above, the compounds of the present invention have the ability to inhibit the activity of ACE, the enzyme which converts angiotensin I to angiotensin II and also inactivates bradykinin. The physiological activity of the compounds of the invention can be evaluated by determining the concentration of the test compound required to inhibit the activity of ACE by 50% in vitro (IC_{50}), for example by the procedure of D.W. Cushman et al. [Biochemical Pharmacology, 20, 1637 (1971)]. Specifically, solutions of ACE extracted from rabbit lungs and, as substrate, hippurylhistidylleucine, to which had been added the test compound at various concentrations, were added to a borate buffer solution containing sodium chloride, and the pH was adjusted to a value of 8.3. The enzymatic reaction was allowed to proceed at 37°C for 30 minutes, after which time the reaction was terminated by adding 1N aqueous hydrochloric acid. The hippuric acid formed by this reaction was extracted with ethyl acetate and the solvent was then distilled from the extract. The residual hippuric acid was dissolved in water. The amount of hippuric acid in the resulting aqueous solution was determined by the absorbency to ultraviolet radiation at 228 nm. The resulting values were then plotted to form a curve indicating the relationship between the amount of hippuric acid formed and the concentration of the test compound. The IC_{50} value can be obtained by reading on this curve the concentration of the test compound which reduces the amount of hippuric acid formed to one half of that formed when no test compound is present. The IC_{50} values obtained for various of the compounds of the invention by this procedure are shown in the following Table. The compounds tested were as follows:

A: α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid (Isomer A-2, product of Example 4);

B: α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetic acid (Isomer B-2, product of Example 5);

C: α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid (product of Example 8).

Table

Test Compound	IC_{50} (moles/litre)
A	1.4×10^{-9}
B	2.0×10^{-9}
C	1.7×10^{-9}

As can be clearly seen from the results in the above Table, the compounds of the invention inhibit ACE activity at very low concentrations and are thus useful as diagnostic, preventative and therapeutic agents for hypertensive patients; likewise, salts of these compounds would have similar activities.

In addition, the compounds of Examples 2, 3, 7, 10 and 12 were tested in vivo. Each of these test compounds was administered orally to rats and its inhibitory effect on angiotensin I-induced hypertension was determined. These compounds all showed strong and lasting inhibitory effects.

For practical, therapeutic use, the compounds of the invention are preferably administered in combination with suitable pharmaceutically acceptable carriers, vehicles or diluents. The compounds can be administered orally or non-orally (e.g. parenterally by intravenous or intramuscular injection) and the form of the composition will, of course, be determined by the intended route of administration. For oral administration, the compounds of the invention may, for example, be administered as powders, granules, tablets, capsules, syrups or elixirs. For parenteral administration, the compounds will be administered in the form of a suitable injectable composition, in which the compound of the invention is dissolved or suspended in a pyrogen-free injectable medium. The dose will vary depending upon the nature and severity of the disorder, as well as upon the age, condition and body weight of the patient. For example, for the therapy of an adult human patient, the dose at each administration would preferably be from 0.5 to 1000 mg, more preferably from 1 to 100 mg, for oral administration, whilst the preferred dose at each administration for intravenous injection is from 0.1 to 100 mg, more preferably from 0.2 to 10 mg. One or more of these doses, preferably from 1 to 3 doses, may be administered daily.

The invention is further illustrated by the following Examples, which describe the preparation of various compounds of the invention, including separation and/or preparation of individual isomers thereof. The values for optical rotation were all measured with the sodium D-line, i.e. all values are $[\alpha]_D$.

EXAMPLE 1

t-Butyl α-{3-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6-phenylperhydroazepin-1-yl}acetate (Compound No. 5)

1(a) Ethyl 5-cyano-5-phenylvalerate

5 g of sodium hydride (as a 55% w/w dispersion in mineral oil) were added slowly to a solution of 11.7 g of phenylacetonitrile and 19.5 g of ethyl 4-bromobutyrate in 150 ml of dimethylformamide, and the reaction mixture was stirred for 4 hours at room temperature. It was then dissolved in ethyl acetate and water. The ethyl acetate layer was separated, washed with an aqueous solution of potassium bisulphate and then with an aqueous solution of sodium chloride, dried over anhydrous magnesium sulphate and concentrated by evaporation under reduced pressure. The oily residue was subjected to silica gel column chromatography using a 1:4 by volume mixture of ethyl acetate and cyclohexane as eluent, to give 13.5 g of the title compound as a colourless liquid.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.22 (3H, triplet, J = 7Hz);
1.7-2.1 (4H, multiplet);
2.2-2.5 (2H, multiplet);
3.7-4.0 (1H, multiplet);
4.12 (2H, quartet. J = 7Hz);
7.33 (5H, singlet).

1(b) Ethyl 6-(t-butoxycarbonylamino)-5-phenylhexanoate

About 10 ml of Raney nickel were added to a solution of 58 g of ethyl 5-cyano-5-phenylvalerate

[prepared as described in step (a) above] in 400 ml of ethanol, and the mixture was stirred for 2.5 hours at 40 °C, under a hydrogen pressure of 3 kg/cm^2. The catalyst was filtered off and the filtrate was condensed to give ethyl 6-amino-5-phenylhexanoate as an oily substance. The whole of this oily substance was dissolved in 300 ml of methylene chloride, and 40 ml of triethylamine were added to the mixture. 55 g of di-t-butyl pyrocarbonate were added to this solution in an ice-bath. The mixture was stirred for 1 hour, and then the solvent was evaporated off under reduced pressure. The residue was dissolved in ethyl acetate and water. The ethyl acetate layer was separated and washed with an aqueous solution of potassium bicarbonate and then with an aqueous solution of sodium chloride. It was then dried over anhydrous magnesium sulphate and the solvent was distilled off under reduced pressure. The residual syrup was mixed with cyclohexane and allowed to stand. The crystals which separated out were collected by filtration as the title product, yield 25 g. The filtrate was condensed and subjected to silica gel column chromatography using a 1:5 by volume mixture of ethyl acetate and cyclohexane as eluent, to give a further 20.5 g of the title compound as crystals, melting at 82-84 °C. Total yield 45.5 g.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.22 (3H, triplet, J = 7Hz);
1.42 (9H, singlet);
1.45-1.75 (4H, multiplet);
2.1-2.4 (2H, multiplet);
2.55-3.75 (3H, multiplet);
4.18 (2H, quartet, J = 7Hz);
4.35 (1H, multiplet);
7.0-7.4 (5H, multiplet).

1(c) 6-Amino-5-phenylhexanoic acid hydrochloride

To 370 ml of an ethanolic suspension containing 37.0 g of ethyl 6-(t-butoxycarbonylamino)-5-phenylhexanoate [prepared as described in step (b) above] were added 79 ml of water containing 8.8 g of sodium hydroxide. The reaction mixture was stirred for 1 hour at room temperature and then the solvent was distilled off under reduced pressure. The residue was mixed with ethyl acetate and water, and the aqueous layer was adjusted to a pH value of 3 by the addition of concentrated hydrochloric acid. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave quantitatively 6-(t-butoxycarbonylamino)-5-phenylhexanoic acid as a syrupy substance.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.39 (9H, singlet);
1.45-1.9 (4H, multiplet);
2.1-2.45 (2H, multiplet);
2.5-3.7 (3H, multiplet);
4.46 (1H, multiplet);
7.0-7.4 (5H, multiplet).

The whole of this syrup was dissolved in 100 ml of a 4N solution of hydrogen chloride in dioxane. The mixture was stirred for 16 hours and then diethyl ether was added to it. The crystals which separated out were collected by filtration to give 27.5 g of the title compound, melting at 163-165.5 °C.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

1.1-1.8 (4H, multiplet);
2.17 (2H, triplet, J = 7Hz);
2.8-3.3 (3H, multiplet);
7.1-7.5 (5H, multiplet).

1(d) 6-Phenylperhydroazepin-2-one

27.6 ml of diphenylphosphoryl azide and then 37.5 ml of N-methylmorpholine were added to 260 ml of dimethylformamide containing 26.0 g of 6-amino-5-phenylhexanoic acid hydrochloride [prepared as described in step (c) above] in an ice-bath. The reaction mixture was stirred for 3.5 hours at room temperature, and then dissolved in 0.5 litre of ethyl acetate and 0.5 litre of water. The ethyl acetate layer was separated, washed with water and dried over anhydrous magnesium sulphate. The solvent was distilled off and the residue was subjected to silica gel column chromatography using a 2:1 by volume mixture of ethyl acetate and methylene chloride as eluent, to give 4.0 g of the title compound as crystals, melting at 153.5-154.5 °C (with decomposition).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.4-2.3 (4H, multiplet);
2.4-2.9 (2H, multiplet);
3.1-3.8 (3H, multiplet);
6.6 (1H, multiplet);
7.0-7.5 (5H, multiplet).

1(e) 3-Bromo-6-Phenylperhydroazepin-2-one

4.4 g of phosphorus pentachloride were added slowly to 60 ml of methylene chloride containing 4.0 g of 6-phenylperhydroazepin-2-one [prepared as described in step (d) above], under a stream of nitrogen, keeping the temperature of the reaction solution at 0 to 5°C. After this addition, the reaction mixture was stirred for 20 minutes, and then 40 mg of iodine, followed by 21.1 ml of a 1M methylene chloride solution of bromine, were dropped into it at 0-5°C. When this addition was complete, the reaction mixture was stirred for 1 hour. The volume of reaction mixture was reduced by half by evaporation under reduced pressure, to separate the title compound as crystals. After the addition of water, the separated crystals were collected by filtration and washed with ethyl acetate, to give 1.8 g of an isomer of the title compound, melting at 218-219.5°C.

This compound is named "Isomer A".

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
1.7-2.25 (4H, multiplet);
2.5-4.0 (3H, multiplet);
4.7 (1H, multiplet);
7.26 (5H, singlet);
7.9 (1H, multiplet).

The filtrate was diluted with methylene chloride, washed with an aqueous solution of sodium thiosulphate and dried over anhydrous magnesium sulphate. The solvent was evaporated and the crystals which separated were collected by filtration and washed with methylene chloride to give 1.1 g of crystals. This product is a mixture of Isomer A and Isomer B.

The resulting filtrate was concentrated further to give 2.6 g of a crystalline substance rich in Isomer B.

1(f) 3(S*)-Azido-6(R*)-phenylperhydroazepin-2-one (Isomer A)

2.0 g of sodium azide were added to 20 ml of dimethylformamide containing 1.6 g of 3-bromo-6-phenylperhydroazepin-2-one (Isomer A) [prepared as described in step (e) above]. The mixture was stirred for 6 hours at 60°C and then diluted with ethyl acetate, washed with water three times and dried over anhydrous magnesium sulphate. The solvent was then distilled off. The crystalline residue was triturated in a 1:1 by volume mixture of methylene chloride and diisopropyl ether and then collected by filtration, to give 1.14 g of the title compound melting at 150-152°C (with decomposition).

Thin layer chromatography on silica gel (developing solvent ethyl acetate-methylene chloride, 1:2 by volume) Rf value = 0.69.

Infrared Absorption Spectrum (Nujol-trade mark-mull) $\nu_{max}cm^{-1}$:
3230, 2100, 1670.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.6-2.2 (4H, multiplet);
2.4-3.0 (1H, multiplet);
3.0-4.4 (3H, multiplet);
7.0-7.4 (5H, multiplet);
7.73 (1H, multiplet).

1(g) 3(S*)-Azido-6(S*)-phenylperhydroazepin-2-one (Isomer B)

Using a similar procedure to that described in Example 1(f), 2.6 g of the crystals rich in Isomer B of 3-bromo-6-phenylperhydroazepin-2-one [prepared from the final filtrate of Example 1(e)] afforded a crude product from which 0.97 g of the title compound was obtained through silica gel column chromatography using a 2:1 by volume mixture of methylene chloride and ethyl acetate as eluent.

Melting point: 122-125°C (with decomposition).

Thin layer chromatography on silica gel (developing solvent ethyl acetate - methylene chloride, 1:2 by volume) Rf value = 0.63.
Infrared Absorption Spectrum (Nujol mull) $\nu_{max}cm^{-1}$:
3220, 2110, 1675.

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
1.75-2.2 (4H, multiplet);
2.4-3.7 (3H, multiplet);
4.35-4.55 (1H, multiplet);
7.1-7.4 (5H, multiplet);
7.96 (1H, multiplet).

1(h) t-Butyl α-[3(S*)-azido-2-oxo-6(R*)-phenylperhydroazepin-1-yl]acetate (Isomer A)

0.9 ml of t-butyl bromoacetate followed by 219 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) were added, under a stream of nitrogen, to a solution of 1.05 g of 3(S*)-azido-6(R*)-phenylperhydroazepin-2-one (Isomer A) [prepared as described in Example 1(f)] in 10 ml of dimethylformamide, whilst ice-cooling. The mixture was stirred for 1.5 hours, and then ethyl acetate and water were added. The ethyl acetate layer was separated, washed with water, and dried over anhydrous magnesium sulphate. The solvent was then distilled off. The residue was purified by silica gel column chromatography using a 1:4 by volume mixture of ethyl acetate and cyclohexane as eluent, to give 1.54 g of the title compound as crystals, melting at 119-121 °C.
Infrared Absorption Spectrum (Nujol mull) $\nu_{max}cm^{-1}$:
2130, 1750, 1660.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.47 (9H, singlet);
1.8-2.3 (4H, multiplet);
2.8-4.6 (4H, multiplet);
4.11 (2H, AB-quartet, $\Delta\delta = 0.33$ ppm, $J = 17Hz$);
7.0-7.5 (5H, multiplet).

1(i) t-Butyl α-[3(S*)-azido-2-oxo-6(S*)-phenylperhydroazepin-1-yl]acetate (Isomer B)

Using a similar procedure to that described in Example 1(h), 1.21 g of 3(S*)-azido-6(S*)-phenylperhydroazepin-2-one (Isomer B) [prepared as described in Example 1(g)], 1 ml of t-butyl bromoacetate and 252 mg of sodium hydride (as a 55% w/w dispersion in mineral oil) afforded 1.9 g of the title compound as a syrup.
Infrared Absorption Spectrum (liquid film) $\nu_{max}cm^{-1}$:
2120, 1740, 1660.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.46 (9H, singlet);
1.8-2.3 (4H, multiplet);
2.8-4.6 (4H, multiplet);
3.98 (2H, AB-quartet, $\Delta\delta = 0.5$ ppm, $J = 17Hz$);
7.0-7.5 (5H, multiplet).

1(i) t-Butyl α-[3(S*)-amino-2-oxo-6(R*)-phenylperhydroazepin-1-yl]acetate (Isomer A)

0.3 g of 5% w/w palladium-on-carbon was added to 30 ml of ethanol containing 1.4 g of t-butyl α-[3(S*)-azido-2-oxo-6(R*)-phenylperhydroazepin-1-yl]acetate (Isomer A) [prepared as described in Example 1(h)], and under one atmosphere pressure of hydrogen the reaction mixture was shaken for 4 hours at 40 °C. The catalyst was filtered off and the solvent was evaporated under reduced pressure, to give 1.56 g of the title compound as a gummy substance.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.47 (9H, singlet);
1.5-2.3 (6H, multiplet);

2.7-4.2 (4H, multiplet);
4.10 (2H, singlet);
7.0-7.5 (5H, multiplet).

1(k) t-Butyl α-[3(S*)-amino-2-oxo-6(S*)-phenylperhydroazepin-1-yl]acetate (Isomer B)

Reduction of 1.9 g of t-butyl α-[3(S*)-azido-2-oxo-6(S*)-phenylperhydroazepin-1-yl]acetate (Isomer B) [prepared as described in Example 1(i)] with 5% w/w palladium-on-carbon in a similar manner to that described in Example 1(j) gave 1.8 g of the title compound as a gummy substance.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.43 & 1.46 (together 9H, each singlet);
1.7-2.3 (4H, multiplet);
2.8-4.5 (6H, multiplet);
3.32 (2H, broad singlet);
7.0-7.4 (5H, multiplet).

1(ℓ) t-Butyl α-{3-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6-phenylperhydroazepin-1-yl]acetate - (Isomer A-1 and Isomer A-2 of Compound No. 5)

0.73 ml of triethylamine followed by 1.80 g of ethyl 4-phenyl-2(R)-trifluoromethanesulphonyloxybutyrate were added to a solution of 1.56 g of t-butyl α-[3(S*)-amino-2-oxo-6(R*)-phenylperhydroazepin-1-yl]acetate (Isomer A) [prepared as described in Example 1(j)] in 20 ml of methylene chloride, in an ice-bath. The reaction solution was allowed to stand for 16 hours at room temperature and then concentrated by evaporation under reduced pressure. The residue was dissolved in ethyl acetate. The solution was washed with water and dried over anhydrous magnesium sulphate, and then the solvent was distilled off. The residue was purified by silica gel column chromatography using a 3:1 by volume mixture of cyclohexane and ethyl acetate as eluent, to give two isomers separately.

The isomer first eluted (Isomer A-1) was a syrup, yield 0.84 g, and has been identified as t-butyl α-(3-(R)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetate.
$[\alpha]_{25}$ -45.3° (C = 1, dimethylformamide).
Thin layer chromatography on silica gel (developing solvent cyclohexane-ethyl acetate, 3:1 by volume) Rf value = 0.49.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.24 (3H, triplet, J = 7Hz);
1.46 (9H, singlet);
1.6-2.3 (7H, multiplet);
2.6-4.0 (7H, multiplet);
4.04 (2H, AB-quartet, Δδ = 0.40 ppm, J = 18Hz);
4.14 (2H, quartet, J = 7Hz);
7.0-7.4 (10H, multiplet).

The isomer next eluted (Isomer A-2) was a syrup, yield 0.95 g, and has been identified as t-butyl α-{3-(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetate.
$[\alpha]_{25}$ +28.1° (C = 1, dimethylformamide).
Thin layer chromatography on silica gel (developing solvent cyclohexane-ethyl acetate, 3:1 by volume) Rf value = 0.40.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.25 (3H, triplet, J = 7Hz);
1.46 (9H, singlet);
1.7-2.3 (7H, multiplet);
2.5-4.1 (7H, multiplet);
4.05 (2H, AB-quartet, Δδ = 0.37 ppm, J = 18Hz);
4.16 (2H, quartet, J = 7Hz);
7.0-7.4 (10H, multiplet).

1(m) t-Butyl α-{3-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6-phenylperhydroazepin-1-yl}acetate - (Isomer B-1 and Isomer B-2 of Compound No. 5)

Using a similar procedure to that described in Example 1(ℓ), 1.87 g of t-butyl α-[3(S*)-amino-2-oxo-6-

(S*)-phenylperhydroazepin-1-yl]acetate (Isomer B) [prepared as described in Example 1(k)] was N-alkylated with 2.45 g of ethyl 4-phenyl-2(R)-trifluoromethanesulphonyloxybutyrate. Isomer B-1 and Isomer B-2 were separated by silica gel column chromatography.

The isomer first eluted (Isomer B-1) was a syrup, yield 1.0 g, and has been identified as t-butyl α-{3(R)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetate.

$[\alpha]_D^{25}$ -29.2° (C = 1, dimethylformamide).

Thin layer chromatography on silica gel (developing solvent cyclohexane-ethyl acetate, 3:1 by volume) Rf value = 0.50.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.25 (3H, triplet, J = 7Hz);
1.44 (9H, singlet);
1.7-2.3 (7H, multiplet);
2.5-4.1 (7H, multiplet);
4.07 (2H, AB-quartet, Δδ = 0.43 ppm, J = 18Hz);
4.16 (2H, quartet, J = 7Hz);
7.24 (10H, singlet).

The isomer next eluted (Isomer B-2) was a syrup, yield 1.2 g, and has been identified as t-butyl α-{3-(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl)acetate.

$[\alpha]_D^{25}$ -11.8° (C = 1, dimethylformamide).

Thin layer chromatography on silica gel (developing solvent cyclohexane-ethyl acetate, 3:1 by volume) Rf value = 0.40.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

1.25 (3H, triplet, J = 7Hz);
1.46 (9H, singlet);
1.7-2.3 (7H, multiplet);
2.6-4.9 (7H, multiplet);
4.07 (2H, AB-quartet, Δδ = 0.34 ppm, J = 18Hz);
4.16 (2H, quartet, J = 7Hz);
7.24 (10H, singlet).

EXAMPLE 2

α-{3(S)-[1(S)-Ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid hydrochloride (Isomer A-2 of Compound No. 2))

4 ml of a 4N hydrogen chloride/dioxane solution in which was dissolved 0.95 g of t-butyl α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetate (Isomer A-2) [prepared as described in Example 1(ℓ)] were allowed to stand for 16 hours; at the end of this time, the solvent was distilled off, and the syrupy residue was mixed with a small amount of ethyl acetate and diisopropyl ether and then filtered, to give 0.80 g of the title compound as a crystalline powder, melting at 200-202° C.

$[\alpha]_D^{25}$ +27.3° (C = 1.1, dimethylformamide).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

1.27 (3H, triplet, J = 7Hz);
1.7-4.9 (15H, multiplet);
4.24 (2H, quartet, J = 7Hz);
7.31 (10H, singlet).

EXAMPLE 3

α-{3(S)-[1(S)-Ethoxycarbonyl-3-phenylpropylaminol-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetic acid hydrochloride (Isomer B-2 of Compound No. 2)

1.2 g of t-butyl α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetate (Isomer B-2) [prepared as described in Example 1(m)] was treated in a similar manner to that described in Example 2, to afford 1.01 g of the title compound as a crystalline powder, melting at 188-190° C.

$[\alpha]_D^{25}$ +48.6° (C = 1.05, dimethylformamide).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:

1.29 (3H, triplet, J = 7Hz);
1.6-4.9 (15H, multiplet);
4.26 (2H, quartet, J = 7Hz);
7.29 (10H, singlet).

EXAMPLE 4

α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid (Isomer A-2 of Compound No. 1)

3.3 ml of a 1N aqueous solution of sodium hydroxide were added to 400 mg of α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid hydrochloride (Isomer A-2) (prepared as described in Example 2). The reaction mixture was then stirred for 7 hours in an ice-bath, after which a 1N aqueous solution of hydrochloric acid was added to adjust its pH to a value of 2.9. The title compound which separated was collected by filtration, yielding 338 mg.
$[\alpha]^{25}$ +37.1° (C = 1.0, 0.1N aqueous NaOH).
Nuclear Magnetic Resonance Spectrum $[(CD_3)_2SO]$ δ ppm:
1.6-2.2 (6H, multiplet);
2.6-4.3 (9H, multiplet);
7.28 (10H, singlet).

EXAMPLE 5

α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetic acid (Isomer B-2 of Compound No. 1)

400 mg of α-{3(1)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2oxo-6(S)-phenylperhydroazepin-1-yl}acetic acid hydrochloride (Isomer B-2) (prepared as described in Example 3) was treated in a similar manner to that described in Example 4, to afford 330 mg of the title compound as a powdery substance.
$[\alpha]^{25}$ +51.7° (C = 1, 0.1N aqueous NaOH).
Nuclear Magnetic Resonance Spectrum $[(CD_3)_2SO]$ δ ppm:
1.6-2.2 (6H, multiplet);
2.6-4.8 (9H, multiplet);
7.1-7.4 (10H, multiplet).

EXAMPLE 6

t-Butyl α-{3-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate (isomer of Compound No. 96)

6(a) 6-(p-Fluorophenyl)perhydroazepin-2-one

The procedure described in Example 1(a)-(d) was repeated, but using p-fluorophenylacetonitrile in place of phenylacetonitrile to give the title compound as crystals, melting at 158-160° C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.5-2.3 (4H, multiplet);
2.4-2.7 (2H, multiplet);
2.7-3.7 (3H, multiplet);
6.8-7.3 (5H, multiplet).

6(b) 3-Bromo-6-(p-fluorophenyl)perhydroazepin-2-one

Using the same procedure as described in Example 1(e), the title compound was prepared as crystals melting at 218° C (with colouration over 210° C) from 6-(p-fluorophenyl)perhydroazepin-2-one [prepared as described in step (a) above].
Nuclear Magnetic Resonance Spectrum $[(CD_3)_2SO]$ δ ppm:
1.7-2.3 (4H, multiplet);
2.5-3.85 (3H, multiplet);

4.71 (1H, multiplet);
7.0-7.4 (4H, multiplet);
7.97 (1H, multiplet).

6(c) 3(S*)-Azido-6(R*)-(p-fluorophenyl)perhydroazepin-2-one

Using a similar procedure to that described in Example 1(f), the title compound was prepared as crystals melting at 103-104.5°C from 3-bromo-6-(p-fluorophenyl)perhydroazepin-2-one [prepared as described in step (b) above].
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.6-2.3 (4H, multiplet);
2.4-2.9 (1H, multiplet);
3.0-3.7 (2H, multiplet);
4.13 (1H, multiplet);
6.8-7.5 (5H, multiplet).

6(d) t-Butyl α-[3(S*)-azido-6(R*)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetate

According to a similar procedure to that described in Example 1(h), 3(S*)-azido-6(R*)-(p-fluorophenyl)-perhydroazepin-2-one [prepared as described in step (c) above] gave the title compound as crystals, melting at 135.5-137°C.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.47 (9H, singlet);
1.75-2.3 (4H, multiplet);
2.8-4.3 (4H):
4.11 (2H, AB-quartet, $\Delta\delta = 0.33$ ppm, $J = 17$Hz);
6.85-7.3 (4H, multiplet).

6(e) t-Butyl α-[3(S*)-amino-6(R*)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetate

According to a similar procedure to that described in Example 1(j), the title compound was prepared as a gum from t-butyl α-[3(S*)-azido-6(R*)-(p-fluorophenyl)-2-oxoperhydrothiazepin-1-yl]acetate [prepared as described in step (d) above].
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.48 (9H, singlet);
1.62 (2H, broad singlet);
1.5-2.3 (4H, multiplet);
2.7-4.1 (4H, multiplet);
4.11 (2H, AB-quartet, $\Delta\delta = 0.32$ ppm, $J = 17$Hz);
6.8-7.3 (4H, multiplet).

6(f) t-Butyl α-{3-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}-acetate

According to a similar procedure to that described in Example 1(ℓ), t-butyl α-[3(S*)-amino-6(R*)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetate [prepared as described in step (e) above] was reacted with ethyl 4-phenyl-2(R)-trifluoromethanesulphonyloxyacetate, to give a crude product, which was subjected to column chromatography through silica gel using a 4:1 by volume mixture of cyclohexane and ethyl acetate as eluent.
t-Butyl α-{3(R)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(S)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate was eluted first.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.26 (3H, triplet, $J = 7$Hz);
1.47 (9H, singlet);
1.7-2.25 (7H, multiplet);
2.6-3.9 (7H, multiplet);
4.09 (2H, AB-quartet, $\Delta\delta = 0.43$ ppm, $J = 17$Hz);
4.18 (2H, quartet, $J = 7$Hz);

6.9-7.3 (4H, multiplet);
7.23 (5H, singlet).

Subsequently, t-butyl α-{3(S)-[1(S)-ehtoxycarbonyl-3-phenylpropylamino]-6(R)(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate was eluted.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
1.28 (3H, triplet, J = 7Hz);
1.47 (9H, singlet);
1.7-2.3 (7H, multiplet);
2.5-4.0 (7H, multiplet);
4.09 (2H, AB-quartet, Δδ = 0.41 ppm, J = 17Hz);
4.18 (2H, quartet, J = 7Hz);
6.85-7.3 (4H, multiplet);
7.23 (5H, singlet).

EXAMPLE 7

α-{3(S)-[1(S)-Ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid hydrochloride (isomer of Compound No. 85, hydrochloride)

According to a similar procedure to that described in Example 2, the title compound, melting at 181-183 °C, was prepared from t-butyl α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate [the second compound to be eluted in Example 6(f)].
$[\alpha]^{25}$ +25.5 ° (C = 1, dimethylformamide).
Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
1.28 (3H, triplet, J = 7Hz);
1.7-4.75 (15H, multiplet);
4.26 (2H, quartet, J = 7Hz);
7.0-7.5 (4H, multiplet);
7.31 (5H, singlet).

EXAMPLE 8

α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid (isomer of Compound No. 84)

According to a similar procedure to that described in Example 4, the title compound was synthesized as a powder from α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid hydrochloride (prepared as described in Example 7).
$[\alpha]^{25}$ +31.4 ° (C = 1, 0.1N aqueous NaOH).
Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
1.6-2.2 (6H, multiplet);
2.5-4.6 (9H, multiplet);
7.0-7.45 (4H, multiplet);
7.28 (5H, singlet).

EXAMPLE 9

t-Butyl α-{3-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}-acetate (isomer of Compound No. 97)

According to a similar procedure to that described in Example 1(ℓ), t-butyl α-[3(S*)-amino-6(R*)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetate [prepared as described in Example 6(e)] was reacted with butyl 4-phenyl-2(R)-trifluoromethanesulphonyloxybutyrate, to give a crude product, which was subjected to column chromatography through silica gel using a 3:1 by volume mixture of cyclohexane and ethyl acetate as eluent.

First, t-butyl α-{3(R)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6(S)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate was eluted.
Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.1 (3H, multiplet);
1.46 (9H, singlet);
1.2-2.2 (10H, multiplet);
2.5-4.2 (9H, multiplet);
4.16 (2H, AB-quartet, $\Delta\delta = 0.33$ ppm, J = 17Hz);
6.9-7.3 (4H, multiplet);
7.22 (5H, singlet).

Subsequently, t-butyl α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate was eluted.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.7-1.1 (3H, multiplet);
1.48 (9H, singlet);
1.2-2.3 (10H, multiplet);
2.5-4.3 (9H, multiplet);
4.09 (2H, AB-quartet, $\Delta\delta = 0.41$ ppm, J = 17Hz);
6.9-7.3 (4H, multiplet);
7.22 (5H, singlet).

EXAMPLE 10

α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid hydrochloride (isomer of Compound No. 86, hydrochloride)

According to a similar procedure to that described in Example 2, the title compound, melting at 207° C, was prepared from t-butyl α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetate [the second compound to be eluted in Example 9].

$[\alpha]_{25}$ -23.4° (C = 1, dimethylformamide).

Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
0.93 (3H, broad triplet, J = 6.5Hz);
1.15-2.4 (10H, multiplet);
2.6-4.75 (11H, multiplet);
7.0-7.5 (4H, multiplet);
7.32 (5H, singlet).

EXAMPLE 11

t-Butyl α-{3-[1(S)-butoxycarbonyl-3-phenylpropylamino]-2-oxo-6-phenylperhydroazepin-1-yl}acetate (isomer of Compound No. 98)

According to a similar procedure to that described in Example 1(ℓ), 1.62 g of t-butyl α-[3(S*)-amino-2-oxo-6(S*)-phenylperhydroazepin-1-yl]acetate [prepared as described in Example 1(j)] was N-alkylated with 2.24 g of butyl 4-phenyl-2-(R)-trifluoromethanesulphonyloxybutyrate, and the resulting product was subjected to silica gel column chromatography, using a 3:1 by volume mixture of cyclohexane and ethyl acetate as eluent.

First, 1.15 g of t-butyl α-{3(R)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(S)-phenylperhydroazepin-1-yl}acetate was obtained as an oil.

$[\alpha]_{25}$ -42.8° (C = 1, dimethylformamide).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:
0.7-1.1 (3H, multiplet);
1.48 (9H, singlet);
1.2-2.25 (10H, multiplet);
2.6-4.25 (9H, multiplet);
4.06 (2H, AB-quartet, $\Delta\delta = 0.42$ ppm, J = 17Hz);
7.26 (10H, singlet).

Then, 1.25 g of t-butyl α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetate was obtained as an oil.

$[\alpha]_{25}$ +28.2° (C = 1, dimethylformamide).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm:

0.7-1.1 (3H, multiplet);
1.47 (9H, singlet);
1.2-2.25 (10H, multiplet);
2.36 (1H, broad singlet);
2.5-4.25 (9H, multiplet);
4.08 (2H, AB-quartet, $\Delta\delta = 0.34$ ppm, J = 17Hz);
7.24 (10H, singlet).

EXAMPLE 12

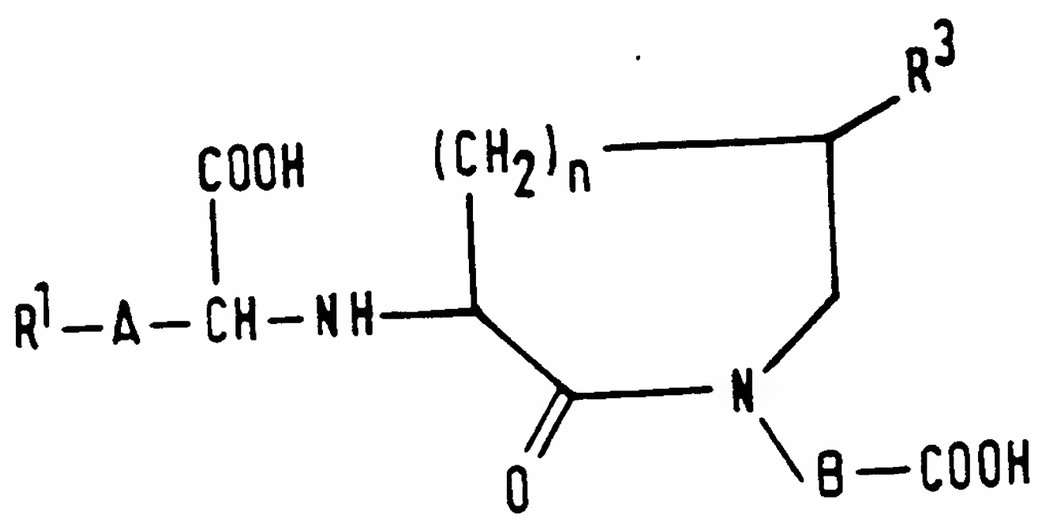
α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl]acetic acid hydrochloride (isomer of Compound No. 3, hydrochloride)

Following the same procedure as described in Example 2, 1.1 g of t-butyl α-{3-[3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetate (the second compound to be eluted in Example 11) gave 0.85 g of the title compound as a crystalline powder, melting at 167-168.5° C.
$[\alpha]_D^{25}$ +25.3° (C = 1, dimethylformamide).
Nuclear Magnetic Resonance Spectrum [$(CD_3)_2SO$] δ ppm:
0.93 (3H, broad triplet, J = 6.5Hz);
1.2-2.5 (10H, multiplet):
2.5-4.75 (11H, multiplet);
7.33 (10H, singlet).

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Compounds of formula (I):

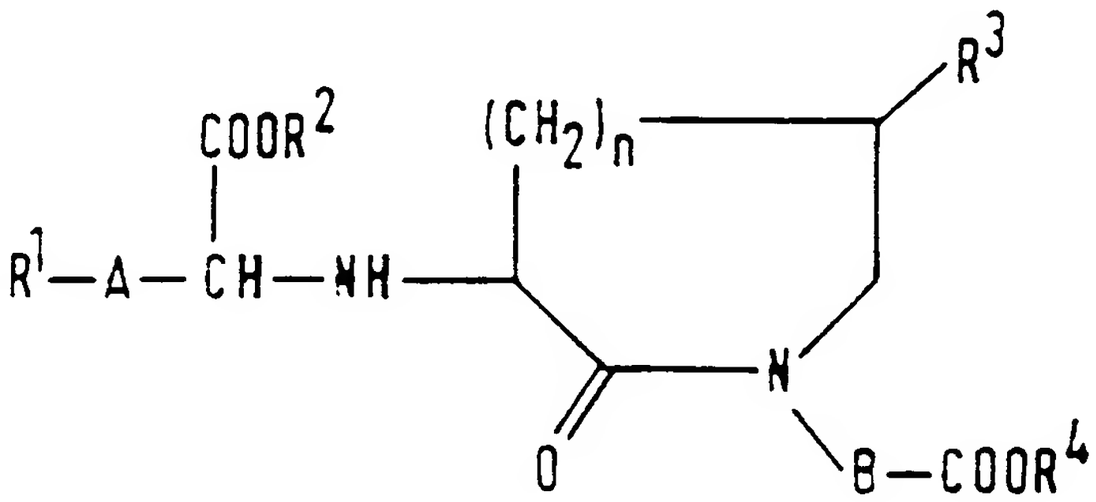


(I)

in which:
R^1 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_6-C_{14} aryl group or a heterocyclic group having from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and/or (b);
R^3 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, an aralkyl group wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl, a C_6-C_{14} aryl group, a C_1-C_6 alkyl group having a heterocyclic substituent or a heterocyclic group, where said heterocyclic group or said heterocyclic substituent has from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and/or (b);
A represents a single bond, a methylene group, an ethylene group or a group of formula -CO-CH_2-, -O-CH_2- or -S-CH_2-;
B represents an alkylene group having from 1 to 4 carbon atoms; and
n is an integer from 1 to 3;

substituents (a):
hydroxy groups, C_1-C_6 alkoxy groups, C_6-C_{10}carbocyclic aryl groups having from 0 to 3 of substituents (a) and/or (b), aralkyloxy groups where the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b), C_6-C_{10} aryloxy groups, halogen atoms, nitro groups, cyano groups, carboxy groups, alkoxycarbonyl groups having a total of from 2 to 7 carbon atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups wherein each alkyl part is C_1-C_6 alkyl, aliphatic or carbocyclic aromatic carboxylic acylamino groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1-C_6 alkyl, dialkylcarbamoyl groups where each alkyl part is C_1-C_6 alkyl, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups and C_6-C_{10} carbocyclic arylsulphonyl groups wherein the aryl part has from 0 to 3 C_1-C_6 alkyl substituents;
substituents (b):
C_1-C_6 alkyl groups and aralkyl groups wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b);
and pharmaceutically acceptable salts and esters thereof.

2. Compounds of formula (Ia):



(Ia)

wherein R^1, R^3, A, B and n are as defined in Claim 1 and R^2 and R^4 are the same or different and each represents a hydrogen atom, a C_1-C_{10} alkyl group, an aralkyl group in which the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or substituted as defined in (c) below and the alkyl part is C_1-C_6 alkyl, a C_6-C_{14} carbocyclic aryl group, a phthalidyl group or a substituted silyl group, said groups represented by R^2 and R^4 being unsubstituted or having at least one substituent selected from:
(c) C_1-C_6 alkyl groups except where the parent group is an alkyl group, halogen atoms, hydroxy groups, C_1-C_6 alkoxy groups, C_1-C_3 alkoxy groups substituted by a C_1-C_6 alkoxy group, aliphatic and carbocyclic aromatic carboxylic acyloxy groups, oxo groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_6 alkoxy, alkoxycarbonyloxy groups where the alkoxy part is C_1-C_6 alkoxy, aliphatic and carbocyclic aromatic carboxylic acylamino groups, nitro groups, cyano groups, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups where each alkyl part is C_1-C_6 alkyl, C_6-C_{10} carbocyclic arylamino groups, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups, C_6-C_{10} carbocyclic arylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur and/or oxygen heteroatoms, said heterocyclic groups being unsubstituted or having at least one of the substituents (a) and/or (b).

3. Compounds as claimed in Claim 2, wherein R^2 represents a hydrogen atom; a straight or branched chain alkyl group having from 1 to 6 carbon atoms; an aralkyl group; or a protecting group which allows the protected carboxy group to be converted easily to a free carboxy group in the living body.

4. Compounds as claimed in Claim 2, wherein R^2 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, acetoxymethyl, pivaloyloxymethyl, phthalidyl, 1-(ethoxycarbonyloxy)ethyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

5. Compounds as claimed in any one of Claims 2 to 4, wherein R^4 represents a t-butyl, methoxymethyl, 2,2,2-trichloroethyl, benzyl, p-methoxybenzyl, diphenylmethyl, acetoxymethyl, pivaloyloxymethyl, 1-

(ethoxycarbonyloxy)ethyl, phthalidyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

6. Compounds as claimed in any one of Claims 1 to 5, wherein:
R^1-A- represents a straight or branched chain alkyl group having from 4 to 9 carbon atoms; a cycloalkylethyl group in which the cycloalkyl part has 5 or 6 ring carbon atoms; an aralkyl group having a total of from 7 to 12 carbon atoms; a phenoxymethyl group; a phenylthiomethyl group; a 2-(2-thienyl)-ethyl group; a 2-(2-imidazolyl)ethyl group; or a 2-(2-thiazolyl)ethyl group;
R^3 represents a straight or branched chain alkyl group having from 1 to 6 carbon atoms; a cycloalkyl group having 5 or 6 ring carbon atoms; an aralkyl group having a total of from 7 to 11 carbon atoms; an aryl group; a heterocyclylmethyl group; or a heterocyclic group;
B represents a methylene group; and
n is 2 or 3.

7. Compounds as claimed in Claim 2, wherein:
R^1 represents a C_4-C_7 alkyl group, a C_5 or C_6 cycloalkyl group, a phenyl group or a phenyl group having at least one substituent selected from the group consisting of substituents (a) and (b);
R^2 represents a hydrogen atom, a C_1-C_4 alkyl group or a benzyl group;
R^3 represents a C_3-C_6 alkyl group, a phenyl group or a phenyl group having at least one substituent selected from the group consisting of substituents (a) and (b);
R^4 represents a hydrogen atom, a C_1-C_4 alkyl group, a benzyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents a C_1 or C_2 alkylene group;
B represents a methylene group; and
n is 2.

8. Compounds as claimed in Claim 2, wherein:
R^1 represents a butyl group, a pentyl group, a hexyl group, a cyclohexyl group or a phenyl group;
R^2 represents a hydrogen atom, a C_2-C_4 alkyl group or a benzyl group;
R^3 represents a phenyl group or a halophenyl group;
R^4 represents a hydrogen atom, a C_2-C_4 alkyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents an ethylene group;
B represents a methylene group; and
n is 2.

9. t-Butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate.

10. α-[3-(1-Ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid.

11. α-[3-(1-Carboxy-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid.

12. t-Butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate.

13. α-[3-(1-Ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid.

14. α-[3-(1-Carboxy-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid.

15. t-Butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate.

16. α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid.

17. t-Butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate.

18. α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid.

19. α-{3(S)-[1(S)-Ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid.

20. α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid.

21. α-{3(S)-[1(S)-Ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid.

22. α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid.

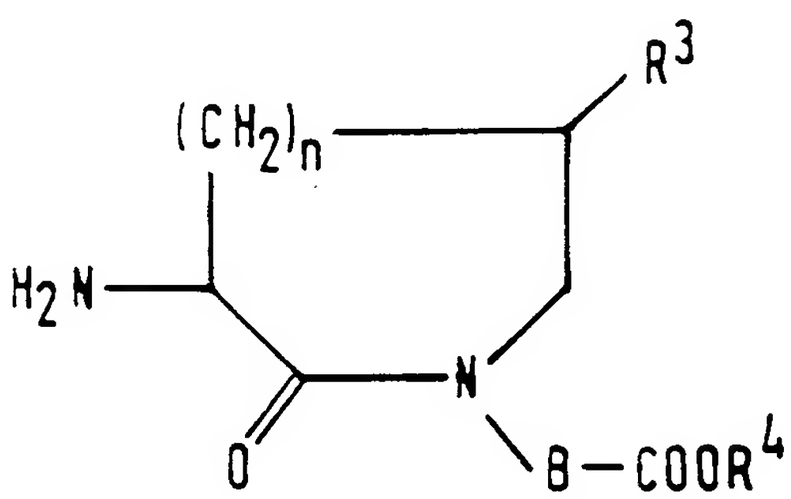
23. α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid.

24. α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid.

25. A pharmaceutical composition for the treatment of angiotensin-induced hypertension, which composition comprises a hypotensive agent in admixture with a pharmaceutically acceptable carrier or diluent, wherein said hypotensive agent is at least one compound as claimed in any one of the preceding Claims.

26. The use for the manufacture of a medicament for the treatment of angiotensin-induced hypertension of a compound as claimed in any one of Claims 1 to 24.

27. A process for preparing a compound as claimed in any one of Claims 1 to 24, which process comprises condensing a compound of formula (II):



(II)

(in which R^3, B and n are as defined in Claim 1 and R^4 is as defined in Claim 2) with a compound of formula (IIIa):

R^1-A-C(=Y)-COOR^2 (IIIa)

(in which: R^1 and A are as defined in Claim 1; Y represents one hydrogen atom and one halogen atom or sulphonyloxy group or, where the condensation is carried out under reductive conditions, a single oxygen atom; and R^2 is as defined in Claim 2) and optionally one or more of the reactions: deprotection, esterification and salification.

28. A process as claimed in Claim 27, wherein said compound of formula (IIIa) has the formula (III):

R^1-A-CH(COOR^2)-X (III)

(in which R^1, A and R^2 are as defined in Claim 27 and X represents a halogen atom or a sulphonyloxy group).

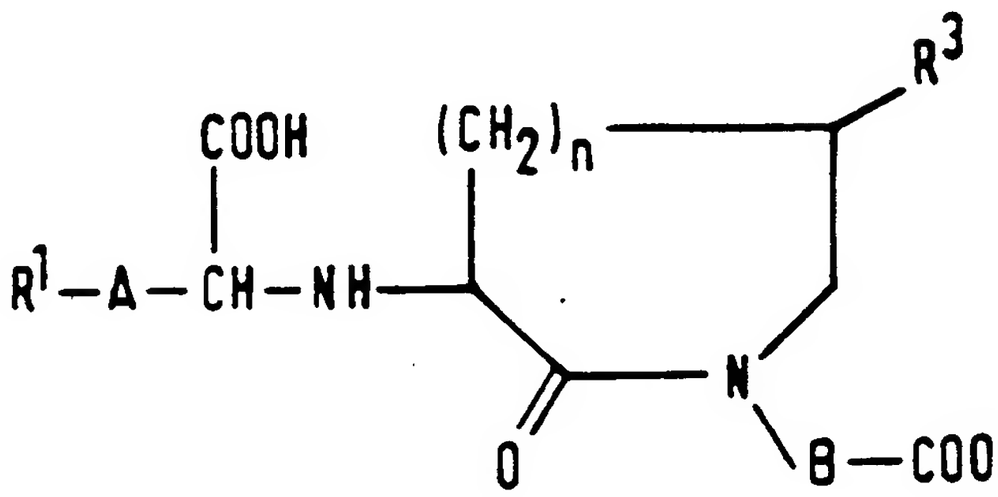
29. A process as claimed in Claim 27, wherein said compound of formula (IIIa) has the formula (IV):

R^1-A-C(=O)-COOR^2 (IV)

(in which R^1, A and R^2 are as defined in Claim 27) and the condensation is carried out under reductive condensation conditions.

Claims for the following Contracting States : AT, ES

1. A process for preparing a compound of formula (I):



(I)

in which:

R^1 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, a C_6-C_{14} aryl group or a heterocyclic group having from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and/or (b);

R^3 represents a C_1-C_{10} alkyl group, a C_3-C_8 cycloalkyl group, an aralkyl group wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl, a C_6-C_{14} aryl group, a C_1-C_6 alkyl group having a heterocyclic substituent or a heterocyclic group, where said heterocyclic group or said heterocyclic substituent has from 4 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, or said alkyl group having at least one of substituents (a) or said cycloalkyl, aryl or heterocyclic group having at least one of substituents (a) and/or (b);

A represents a single bond, a methylene group, an ethylene group or a group of formula -CO-CH_2-, -O-CH_2- or -S-CH_2-;

B represents an alkylene group having from 1 to 4 carbon atoms; and

n is an integer from 1 to 3;

substituents (a):

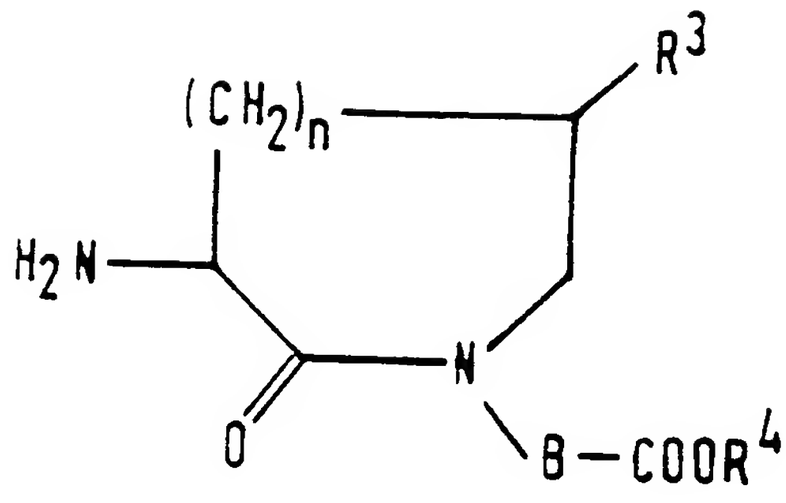
hydroxy groups, C_1-C_6 alkoxy groups, C_6-C_{10} carbocyclic aryl groups having from 0 to 3 of substituents (a) and/or (b), aralkyloxy groups where the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b), C_6-C_{10} aryloxy groups, halogen atoms, nitro groups, cyano groups, carboxy groups, alkoxycarbonyl groups having a total of from 2 to 7 carbon atoms, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups wherein each alkyl part is C_1-C_6 alkyl, aliphatic or carbocyclic aromatic carboxylic acylamino groups, carbamoyl groups, alkylcarbamoyl groups where the alkyl part is C_1-C_6 alkyl, dialkylcarbamoyl groups where each alkyl part is C_1-C_6 alkyl, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups and C_6-C_{10} carbocyclic arylsulphonyl groups wherein the aryl part has from 0 to 3 C_1-C_6 alkyl substituents;

substituents (b):

C_1-C_6 alkyl groups and aralkyl groups wherein the alkyl part is C_1-C_6 alkyl and the aryl part is C_6-C_{10} carbocyclic aryl which has from 0 to 3 of substituents (a) and/or (b);

or a pharmaceutically acceptable salt or ester thereof,

which process comprises condensing a compound of formula (II):



(II)

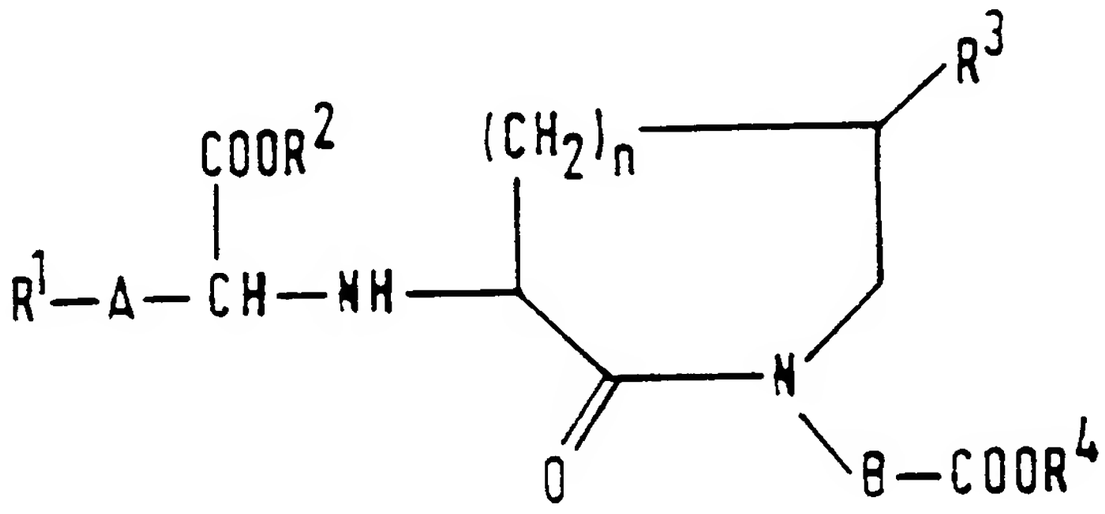
(in which R^3, B and n are as defined above and R^4 represents a hydrogen atom, a C_1-C_{10} alkyl group, an aralkyl group in which the aryl part is a C_6-C_{10} carbocyclic aryl group which is unsubstituted or substituted as defined in (c) below and the alkyl part is C_1-C_6 alkyl, a C_6-C_{14} carbocyclic aryl group, a phthalidyl group or a substituted silyl group, said groups represented by R^4 being unsubstituted or having at least one substituent selected from:

(c) C_1-C_6 alkyl groups except where the parent group is an alkyl group, halogen atoms, hydroxy groups, C_1-C_6 alkoxy groups, C_1-C_3 alkoxy groups substituted by a C_1-C_6 alkoxy group, aliphatic and carbocyclic aromatic carboxylic acyloxy groups, oxo groups, carboxy groups, alkoxycarbonyl groups where the alkoxy part is C_1-C_6 alkoxy, alkoxycarbonyloxy groups where the alkoxy part is C_1-C_6 alkoxy, aliphatic and carbocyclic aromatic carboxylic acylamino groups, nitro groups, cyano groups, amino groups, C_1-C_6 alkylamino groups, dialkylamino groups where each alkyl part is C_1-C_6 alkyl, C_6-C_{10} carbocyclic arylamino groups, mercapto groups, C_1-C_6 alkylthio groups, C_6-C_{10} carbocyclic arylthio groups, C_1-C_6 alkylsulphonyl groups, C_6-C_{10} carbocyclic arylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur and/or oxygen hetero-atoms, said heterocyclic groups being unsubstituted or having at least one of substituents (a) and/or (b), with a compound of formula (IIIa):

$$R^1\text{-A-C}(=Y)\text{-COOR}^2 \qquad \text{(IIIa)}$$

(in which: R^1 and A are as defined above; Y represents one hydrogen atom and one halogen atom or sulphonyloxy group or, where the condensation is carried out under reductive conditions, a single oxygen atom; and R^2 is as defined for R^4, above and is the same or different from R^4) and optionally one or more of the reactions: deprotection, esterification and salification.

2. A process as claimed in Claim 1, wherein there is prepared a compound having the formula (Ia):



(Ia)

wherein R^1, R^2, R^3, R^4, A, B and n are as defined in Claim 1.

3. A process as claimed in Claim 2, wherein R^2 represents a hydrogen atom; a straight or branched chain alkyl group having from 1 to 6 carbon atoms; an aralkyl group; or a protecting group which allows the protected carboxy group to be converted easily to a free carboxy group in the living body.

4. A process as claimed in Claim 2, wherein R^2 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, acetoxymethyl, pivaloyloxymethyl, phthalidyl, 1-(ethoxycarbonyloxy)ethyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

5. A process as claimed in any one of Claims 2 to 4, wherein R^4 represents a t-butyl, methoxymethyl, 2,2,2-trichloroethyl, benzyl, p-methoxybenzyl, diphenylmethyl, acetoxymethyl, pivaloyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, phthalidyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

6. A process as claimed in any one of Claims 1 to 5, wherein:
R^1-A- represents a straight or branched chain alkyl group having from 4 to 9 carbon atoms; a cycloalkylethyl group in which the cycloalkyl part has 5 or 6 ring carbon atoms; an aralkyl group having a total of from 7 to 12 carbon atoms; a phenoxymethyl group; a phenylthiomethyl group; a 2-(2-thienyl)-ethyl group; a 2-(2-imidazolyl)ethyl group; or a 2-(2-thiazolyl)ethyl group;
R^3 represents a straight or branched chain alkyl group having from 1 to 6 carbon atoms; a cycloalkyl group having 5 or 6 ring carbon atoms; an aralkyl group having a total of from 7 to 11 carbon atoms; an aryl group; a heterocyclylmethyl group; or a heterocyclic group;
B represents a methylene group; and
n is 2 or 3.

7. A process as claimed in Claim 2, wherein:
R^1 represents a C_4-C_7 alkyl group, a C_5 or C_6 cycloalkyl group, a phenyl group or a phenyl group having at least one of substituents (a) and/or (b);
R^2 represents a hydrogen atom, a C_1-C_4 alkyl group or a benzyl group;
R^3 represents a C_3-C_6 alkyl group, a phenyl group or a phenyl group having at least one of substituents (a) and/or (b);
R^4 represents a hydrogen atom, a C_1-C_4 alkyl group, a benzyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents a C_1 or C_2 alkylene group;
B represents a methylene group; and
n is 2.

8. A process as claimed in Claim 2, wherein:
R^1 represents a butyl group, a pentyl group, a hexyl group, a cyclohexyl group or a phenyl group;
R^2 represents a hydrogen atom, a C_2-C_4 alkyl group or a benzyl group;
R^3 represents a phenyl group or a halophenyl group;
R^4 represents a hydrogen atom, a C_2-C_4 alkyl group, a p-methoxybenzyl group or a diphenylmethyl group;
A represents an ethylene group;
B represents a methylene group; and
n is 2.

9. A process as claimed in Claim 1, wherein the reagents and reaction conditions are so selected as to prepare:
t-butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate;
α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
α-[3-(1-carboxy-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate;
α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
α-[3-(1-carboxy-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate;
α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate;
α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-

yl}acetic acid;
α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid;
or
α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid.

10. A process as claimed in any one of Claims 1 to 9, wherein said compound of formula (IIIa) has the formula (III):

R^1-A-CH($COOR^2$)-X (III)

(in which R^1, A and R^2 are as defined in Claim 1 and X represents a halogen atom or a sulphonyloxy group).

11. A process as claimed in any one of Claims 1 to 9, wherein said compound of formula (IIIa) has the formula (IV):

R^1-A-C(=O)-$COOR^2$ (IV)

(in which R^1, A and R^2 are as defined in Claim 1) and the condensation is carried out under reductive condensation conditions.

12. The use for the manufacture of a medicament for the treatment of hypertension of a compound of formula (I), as defined in Claim 1, or a pharmaceutically acceptable salt or ester thereof.

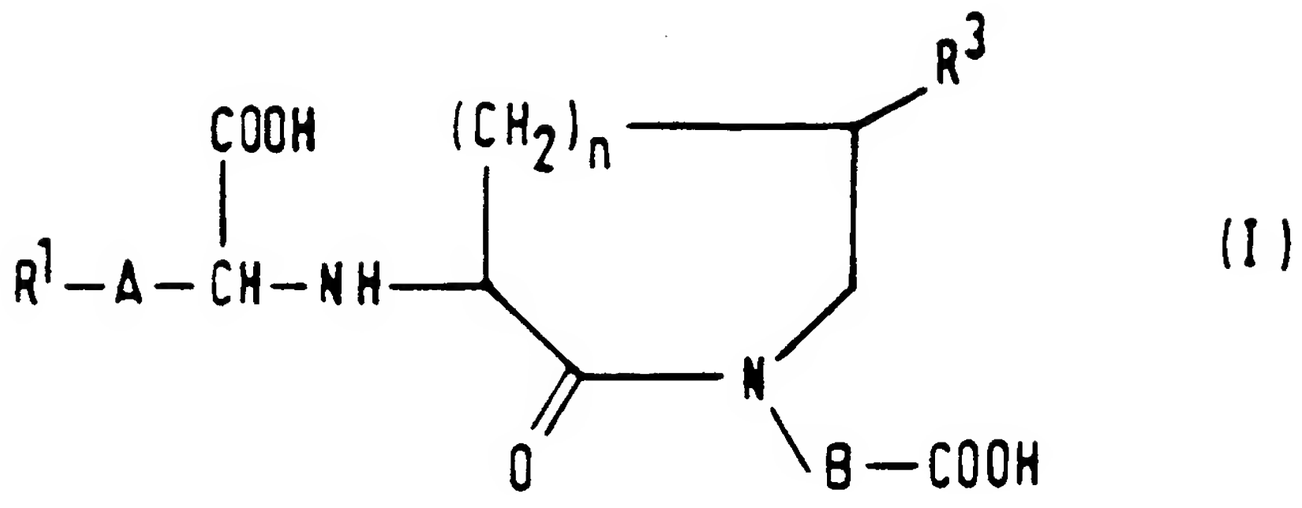
13. The use for the manufacture of a medicament for the treatment of hypertension of a compound of formula (Ia), as defined in Claim 2, or a pharmaceutically acceptable salt thereof.

14. The use as claimed in Claim 12, wherein said compound is:
t-butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate;
α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
α-[3-(1-carboxy-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate;
α-[3-(1-ethoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
α-[3-(1-carboxy-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]-acetate;
α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl]acetic acid;
t-butyl α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetate;
α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetic acid;
α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-carboxy-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid;
α-{3(S)-[1(S)-butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorophenyl)-2-oxoperhydroazepin-1-yl}acetic acid;
or
α-{3(S)-[1(S-)butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}acetic acid.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés de formule (I) :



(I)

dans laquelle :

R^1 représente un groupe alkyle en C_1-C_{10}, un groupe cycloalkyle en C_3-C_8, un groupe aryle en C_6-C_{14} ou un groupe hétérocyclique ayant de 4 à 14 atomes formant le cycle, dont 1 à 5 sont des hétéro-atomes d'azote et/ou d'oxygène et/ou de soufre, ou ledit groupe alkyle ayant au moins un des substituants (a) ou ledit groupe cycloalkyle, aryle ou hétérocyclique ayant au moins un des substituants (a) et/ou (b) ;

R^3 représente un groupe alkyle en C_1-C_{10}, un groupe cycloalkyle en C_3-C_8, un groupe aralkyle dont la partie alkyle est un fragment alkyle en C_1 -C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10}, un groupe aryle en C_6-C_{14}, un groupe alkyle en C_1-C_6 ayant un substituant hétérocyclique, ou un groupe hétérocyclique, où ledit groupe hétérocyclique ou ledit substituant hétérocyclique a de 4 à 14 atomes formant le cycle, dont l à 5 sont des hétéro-atomes d'azote et/ou d'oxygène et/ou de soufre, ou ledit groupe alkyle ayant au moins un des substituants (a) ou ledit groupe cycloalkyle, aryle ou hétérocyclique ayant au moins un des substituants (a) et/ou (b) ;

A représente une simple liaison, un groupe méthylène, un groupe éthylène ou un groupe de formule -CO-CH_2-, -O-CH_2- ou -S-CH_2- ;

B représente un groupe alkylène ayant de 1 à 4 atomes de carbone ; et

n est un entier de 1 à 3 ;

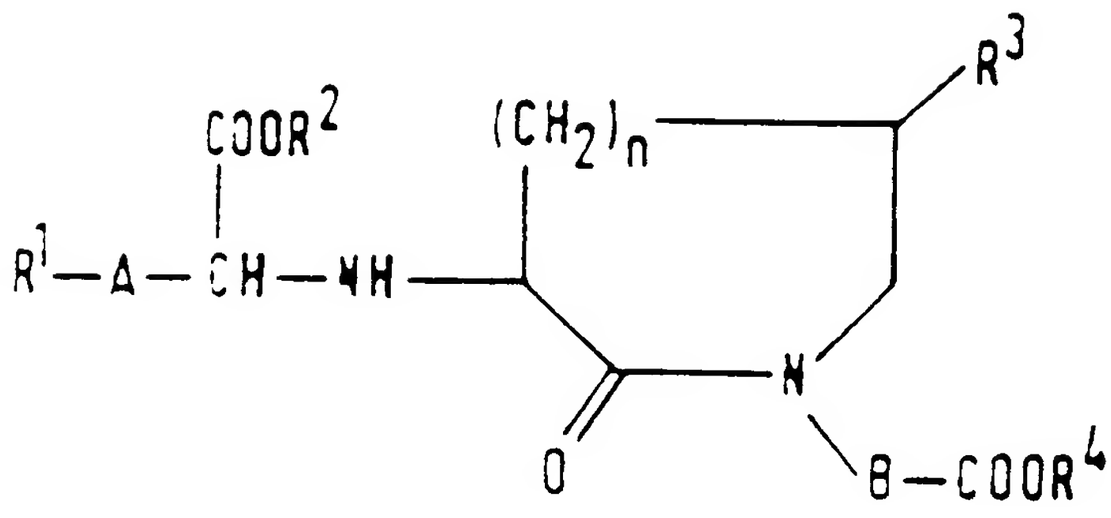
substituants (a) :

groupes hydroxy, groupes alcoxy en C_1-C_6, groupes aryle carbocycliques en C_6-C_{10} ayant de 0 à 3 substituants (a) et/ou (b), groupes aralkyloxy dont la partie alkyle est un fragment alkyle en C_1-C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10} qui a de 0 à 3 substituants (a) et/ou (b), groupes aryloxy en C_6-C_{10}, atomes d'halogène, groupes nitro, groupes cyano, groupes carboxy, groupes alcoxycarbonyle ayant au total de 2 à 7 atomes de carbone, groupes amino, groupes alkylamino en C_1-C_6, groupes dialkylamino dont chaque partie alkyle est un fragment alkyle en C_1-C_6, groupes acylamino carboxyliques aliphatiques ou carbocycliques aromatiques, groupes carbamoyle, groupes alkylcarbamoyle dont la partie alkyle est un fragment alkyle en C_1-C_6, groupes dialkylcarbamoyle dont chaque partie alkyle est un fragment alkyle en C_1-C_6, groupes mercapto, groupes alkylthio en C_1-C_6, groupes arylthio carbocycliques en C_6-C_{10}, groupes alkylsulfonyle en C_1-C_6 et groupes arylsulfonyle carbocycliques en C_6-C_{10} dont la partie aryle a de 0 à 3 substituants alkyle en C_1-C_6 ;

substituants (b) :

groupes alkyle en C_1-C_6 et groupes aralkyle dont la partie alkyle est un fragment alkyle en C_1-C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10} qui a de 0 à 3 substituants (a) et/ou (b) ; et leurs sels et esters pharmaceutiquement acceptables.

2. Composés de formule (Ia) :



(Ia)

dans laquelle R^1, R^3, A, B et n sont comme définis dans la revendication 1 et R^2 et R^4 sont semblables ou différents et représentent chacun un atome d'hydrogène, un groupe alkyle en C_1-C_{10}, un groupe aralkyle dont la partie aryle est un groupe aryle carbocyclique en C_6-C_{10} qui est non substitué ou substitué, comme défini en (c) ci-dessous, et la partie alkyle est un groupe alkyle en C_1-C_6, un groupe aryle carbocyclique en C_6-C_{14}, un groupe phtalidyle ou un groupe silyle substitué, lesdits groupes représentés par R^2 et R^4 étant non substitués ou ayant au moins un substituant choisi parmi :
(c) les groupes alkyle en C_1-C_6 sauf lorsque le groupe parent est un groupe alkyle, les atomes d'halogène, les groupes hydroxy, les groupes alcoxy en C_1-C_6, les groupes alcoxy en C_1-C_3 substitués par un groupe alcoxy en C_1-C_6, les groupes acyloxy carboxyliques aliphatiques et carbocycliques aromatiques, les groupes oxo, les groupes carboxy, les groupes alcoxycarbonyle dont la partie alcoxy est un fragment alcoxy en C_1-C_6, les groupes alcoxycarbonyloxy dont la partie alcoxy est un fragment alcoxy en C_1-C_6, les groupes acylamino carboxyliques aliphatiques et carbocycliques aromatiques, les groupes nitro, les groupes cyano, les groupes amino, les groupes alkylamino en C_1-C_6, les groupes dialkylamino dont chaque partie alkyle est un fragment alkyle en C_1-C_6, les groupes arylamino carbocycliques en C_6-C_{10}, les groupes mercapto, les groupes alkylthio en C_1-C_6, les groupes arylthio carbocycliques en C_6-C_{10}, les groupes alkylsulfonyle en C_1-C_6, les groupes arylsulfonyle carbocycliques en C_6-C_{10} et les groupes hétérocycliques ayant de 5 à 14 atomes formant le cycle, dont 1 à 5 sont des hétéro-atomes d'azote et/ou de soufre et/ou d'oxygène, lesdits groupes hétérocycliques étant non substitués ou ayant au moins un des substituants (a) et/ou (b).

3. Composés selon la revendication 2, dans lesquels R^2 représente un atome d'hydrogène ; un groupe alkyle à chaîne droite ou ramifiée ayant de 1 à 6 atomes de carbone ; un groupe aralkyle ; ou un groupe protecteur qui permet la conversion facile du groupe carboxy protégé en un groupe carboxy libre dans l'organisme vivant.

4. Composés selon la revendication 2, dans lesquels R^2 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle, hexyle, benzyle, acétoxyméthyle, pivaloyloxyméthyle, phtalidyle, 1-(éthoxycarbonyloxy)éthyle ou (5-méthyl-2-oxo-1,3-dioxolène-4-yl)-méthyle.

5. Composés selon l'une quelconque des revendications 2 à 4, dans lesquels R^4 représente un groupe tert-butyle, méthoxyméthyle, 2,2,2-trichloroéthyle, benzyle, p-méthoxybenzyle, diphénylméthyle, acétoxyméthyle, pivaloyloxyméthyle, 1-(éthoxycarbonyloxy)éthyle, phtalidyle ou (5-méthyl-2-oxo-1,3-dioxolène-4-yl)méthyle.

6. Composés selon l'une quelconque des revendications 1 à 5, dans lesquels :
R^1-A- représente un groupe alkyle à chaîne droite ou ramifiée ayant de 4 à 9 atomes de carbone ; un groupe cycloalkyléthyle dont la partie cycloalkyle a 5 ou 6 atomes de carbone formant le cycle ; un groupe aralkyle ayant au total de 7 à 12 atomes de carbone ; un groupe phénoxyméthyle ; un groupe phénylthiométhyle ; un groupe 2-(2-thiényl)éthyle ; un groupe 2-(2-imidazolyl)éthyle ; ou un groupe 2-(2-thiazolyl)éthyle ;
R^3 représente un groupe alkyle à chaîne droite ou ramifiée ayant de 1 à 6 atomes de carbone ; un groupe cycloalkyle ayant 5 ou 6 atomes de carbone formant le cycle ; un groupe aralkyle ayant au total 7 à 11 atomes de carbone ; un groupe aryle ; un groupe hétérocyclylméthyle ; ou un groupe

hétérocyclique ;
B représente un groupe méthylène ; et
n est 2 ou 3.

7. Composés selon la revendication 2, dans lesquels :
R^1 représente un groupe alkyle en C_4-C_7, un groupe cycloalkyle en C_5 ou C_6, un groupe phényle ou un groupe phényle ayant au moins un substituant choisi parmi les substituants (a) et (b) ;
R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_4 ou un groupe benzyle ;
R^3 représente un groupe alkyle en C_3-C_6, un groupe phényle ou un groupe phényle ayant au moins un substituant choisi parmi les substituants (a) et (b);
R^4 représente un atome d'hydrogène, un groupe alkyle en C_1-C_4, un groupe benzyle, un groupe p-méthoxybenzyle ou un groupe diphénylméthyle ;
A représente un groupe alkylène en C_1 ou C_2 ;
B représente un groupe méthylène ; et
n est 2.

8. Composés selon la revendication 2, dans lesquels :
R^1 représente un groupe butyle, un groupe pentyle, un groupe hexyle, un groupe cyclohexyle ou un groupe phényle ;
R^2 représente un atome d'hydrogène, un groupe alkyle en C_2-C_4 ou un groupe benzyle ;
R^3 représente un groupe phényle ou un groupe halogénophényle ;
R^4 représente un atome d'hydrogène, un groupe alkyle en C_2-C_4, un groupe p-méthoxybenzyle ou un groupe diphénylméthyle ;
A représente un groupe éthylène ;
B représente un groupe méthylène ; et
n est 2.

9. α-(3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétate de tert-butyle.

10. Acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique.

11. Acide α-[3-(1-carboxy-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique.

12. α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de tert-butyle.

13. Acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique.

14. Acide α-[3-(1-carboxy-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétique.

15. α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de tert-butyle.

16. Acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique.

17. α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl)acétate de tert-butyle.

18. Acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique.

19. Acide α-{3(S)-[1(S)-éthoxycarbonyl-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique.

20. Acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl)acétique.

21. Acide α-{3(S)-(1(S)-éthoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique.

22. Acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique.

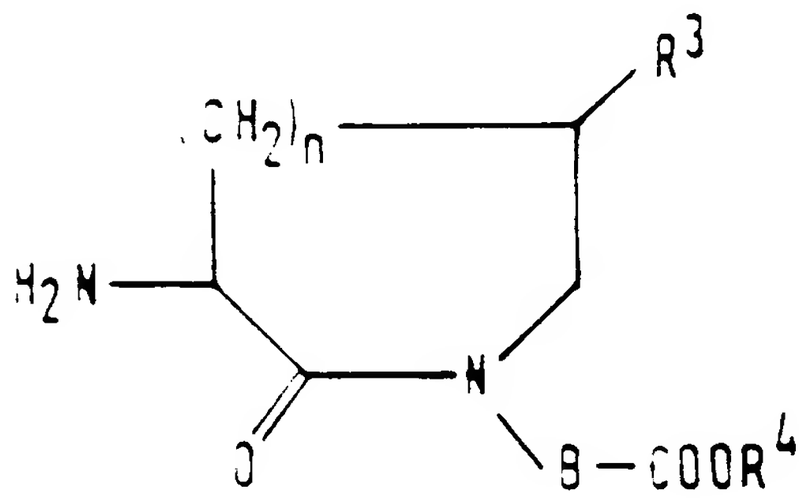
23. Acide α-{3(S)[1(S)-butoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique.

24. Acide α-(3(S)-(1(S)-butoxycarbonyl-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl)-acétique.

25. Composition pharmaceutique pour le traitement de l'hypertension induite par l'angiotensine, laquelle composition comprend un agent hypotenseur en mélange avec un véhicule ou diluant pharmaceutiquement acceptables, dans laquelle ledit agent hypotenseur est au moins un composé selon l'une quelconque des revendications précédentes.

26. Emploi pour la préparation d'un médicament pour le traitement de l'hypertension induite par l'angiotensine d'un composé selon l'une quelconque des revendications 1 à 24.

27. Procédé pour préparer un composé selon l'une quelconque des revendications 1 à 24 qui comprend la condensation d'un composé de formule (II) :



(II)

(dans laquelle R^3, B et n sont comme définis dans la revendication 1 et R^4 est comme défini dans la revendication 2) avec un composé de formule (IIIa) :

R^1-A-C(=Y)-COOR^2 (IIIa)

(dans laquelle R^1 et A sont comme définis dans la revendication 1 ; Y représente un atome d'hydrogène et un atome d'halogène ou un groupe sulfonyloxy ou, lorsque la condensation est effectuée dans des conditions réductrices, un atome d'oxygène unique ; et R^2 est comme défini dans la revendication 2) et facultativement une ou plusieurs des réactions de déprotection, estérification et salification.

28. Procédé selon la revendication 27, dans lequel ledit composé de formule (IIIa) répond à la formule (III) :

R^1-A-CH(COOR^2)-X (III)

(dans laquelle R^1, A et R^2 sont comme définis dans la revendication 27 et x représente un atome d'halogène ou un groupe sulfonyloxy).

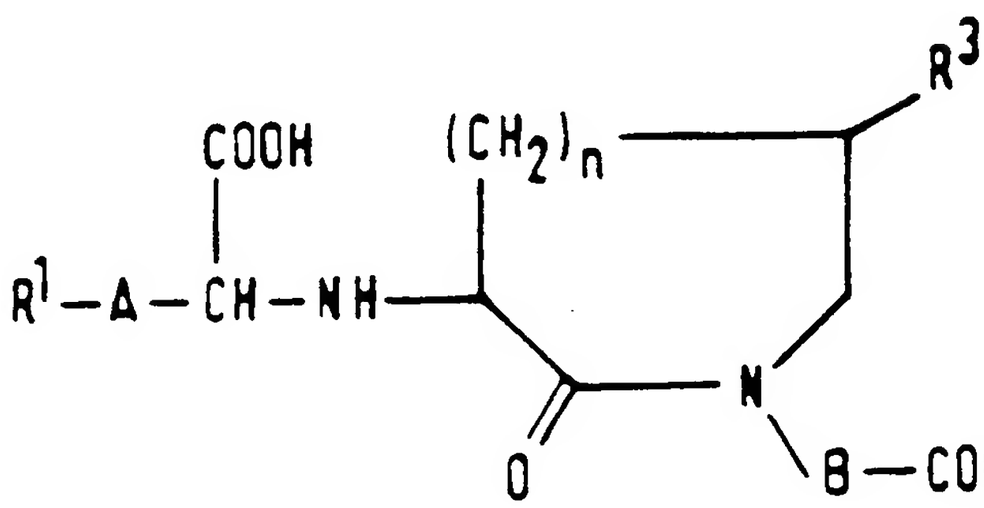
29. Procédé selon la revendication 27, dans lequel ledit composé de formule (IIIa) répond à la formule (IV) :

R^1-A-C(=O)-COOR^2 (IV)

(dans laquelle R^1, A et R^2 sont comme définis dans la revendication 27) et la condensation est effectuée dans des conditions de condensation réductrices.

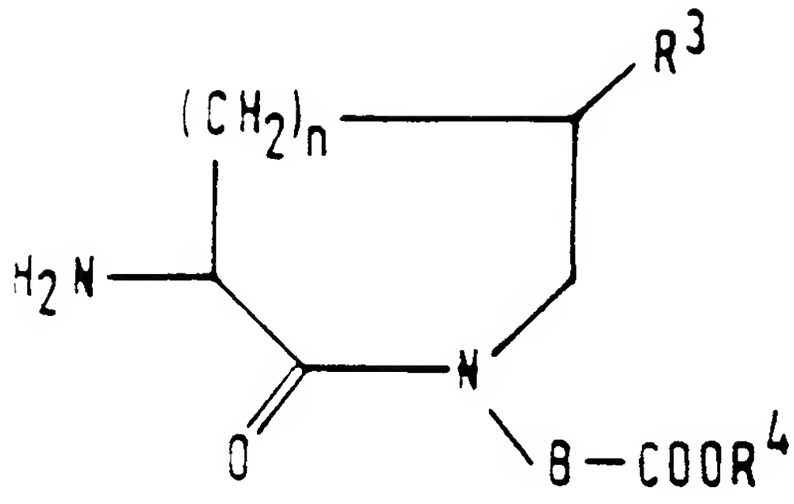
Revendications pour les Etats contractants suivants : AT, ES

1. Procédé de préparation d'un composé de formule (I) :



(I)

dans laquelle :
R^1 représente un groupe alkyle en C_1-C_{10}, un groupe cycloalkyle en C_3-C_8, un groupe aryle en C_6-C_{14} ou un groupe hétérocyclique ayant de 4 à 14 atomes formant le cycle, dont 1 à 5 sont des hétéro-atomes d'azote et/ou d'oxygène et/ou de soufre, ou ledit groupe alkyle ayant au moins un des substituants (a) ou ledit groupe cycloalkyle, aryle ou hétérocyclique ayant au moins un des substituants (a) et/ou (b) ;
R^3 représente un groupe alkyle en C_1 -C_{10}, un groupe cycloalkyle en C_3-C_8, un groupe aralkyle dont la partie alkyle est un fragment alkyle en C_1-C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10}, un groupe aryle en C_6-C_{14} un groupe alkyle en C_1-C_6 ayant un substituant hétérocyclique ou un groupe hétérocyclique, où ledit groupe hétérocyclique ou ledit substituant hétérocyclique a de 4 à 14 atomes formant le cycle, dont 1 à 5 sont des hétéro-atomes d'azote et/ou d'oxygène et/ou de soufre, ou ledit groupe alkyle ayant au moins un des substituants (a) ou ledit groupe cycloalkyle, aryle ou hétérocyclique ayant au moins un des substituants (a) et/ou (b) ;
A représente une simple liaison, un groupe méthylène, un groupe éthyène ou un groupe de formule -CO-CH_2-, -O-CH_2- ou -S-CH_2- ;
B représente un groupe alkylène ayant de 1 à 4 atomes de carbone ; et
n est un entier de 1 à 3 ;
substituants (a) :
groupes hydroxy, groupes alcoxy en C_1-C_6, groupes aryle carbocycliques en C_6-C_{10} ayant de 0 à 3 substituants (a) et/ou (b), groupes aralkyloxy dont la partie alkyle est un fragment alkyle en C_1-C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10} qui a de 0 à 3 substituants (a) et/ou (b), groupes aryloxy en C_6-C_{10}, atomes d'halogène, groupes nitro, groupes cyano, groupes carboxy, groupes alcoxycarbonyle ayant au total de 2 à 7 atomes de carbone, groupes amino, groupes alkylamino en C_1-C_6, groupes dialkylamino dont chaque partie alkyle est un fragment alkyle en C_1-C_6, groupes acylamino carboxyliques aliphatiques ou carbocycliques aromatiques, groupes carbamoyle, groupes alkylcarbamoyle dont la partie alkyle est un fragment alkyle en C_1-C_6, groupes dialkylcarbamoyle dont chaque partie alkyle est un fragment alkyle en C_1-C_6, groupes mercapto, groupes alkylthio en C_1-C_6, groupes arylthio carbocycliques en C_6-C_{10}, groupes alkylsulfonyle en C_1-C_6 et groupes arylsulfonyle carbocycliques en C_6-C_{10} dont la partie aryle a de 0 à 3 substituants alkyle en C_1-C_6 ;
substituants (b) :
groupes alkyle en C_1-C_6 et groupes aralkyle dont la partie alkyle est un fragment alkyle en C_1-C_6 et la partie aryle est un fragment aryle carbocyclique en C_6-C_{10} qui a de 0 à 3 substituants (a) et/ou (b) ; ou un sel ou ester pharmaceutiquement acceptables de celui-ci, qui comprend la condensation d'un composé de formule (II) :



(II)

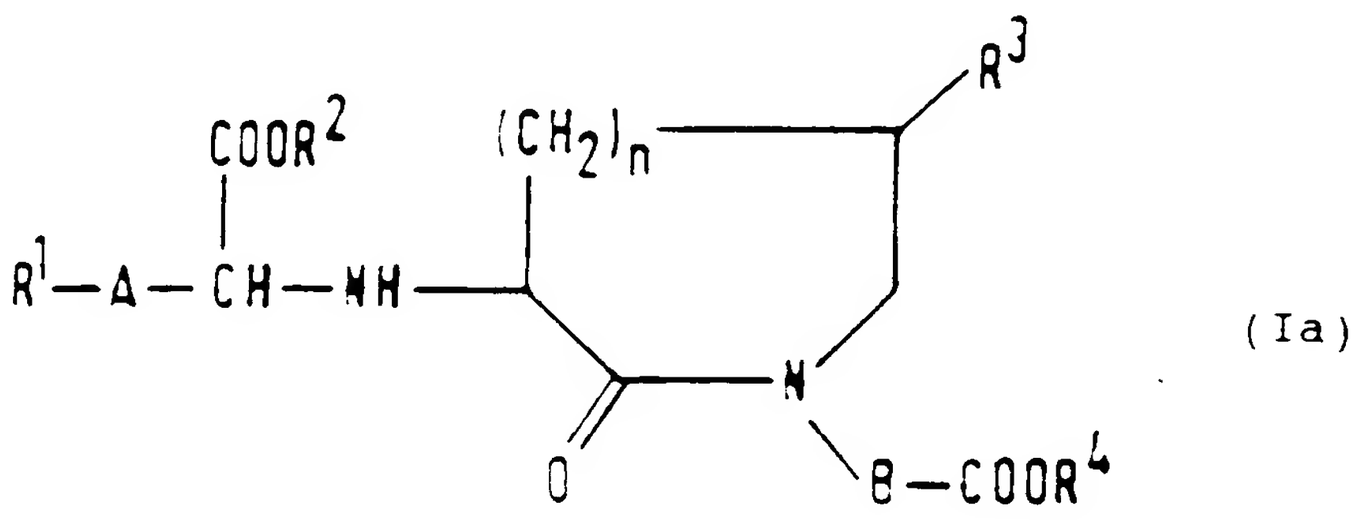
(dans laquelle R^3, B et n sont comme définis ci-dessus et R^4 représente un atome d'hydrogène, un groupe alkyle en C_1-C_{10}, un groupe aralkyle dont la partie aryle est un groupe aryle carbocyclique en C_6-C_{10} qui est non substitué ou substitué, comme défini en (c) ci-dessous, et la partie alkyle est un groupe alkyle en C_1-C_6, un groupe aryle carbocyclique en C_6-C_{14}, un groupe phtalidyle ou un groupe silyle substitué, lesdits groupes représentés par R^2 et R^4 étant non substitués ou ayant au moins un substituant choisi parmi :

(c) les groupes alkyle en C_1-C_6 sauf lorsque le groupe parent est un groupe alkyle, les atomes d'halogène, les groupes hydroxy, les groupes alcoxy en C_1-C_6, les groupes alcoxy en C_1-C_3 substitués par un groupe alcoxy en C_1-C_6, les groupes acyloxy carboxyliques aliphatiques et carbocycliques aromatiques, les groupes oxo, les groupes carboxy, les groupes alcoxycarbonyle dont la partie alcoxy est un fragment alcoxy en C_1-C_6, les groupes alcoxycarbonyloxy dont la partie alcoxy est un fragment alcoxy en C_1-C_6, les groupes acylamino carboxyliques aliphatiques et carbocycliques aromatiques, les groupes nitro, les groupes cyano, les groupes amino, les groupes alkylamino en C_1-C_6, les groupes dialkylamino dont chaque partie alkyle est un fragment alkyle en C_1-C_6, les groupes arylamino carbocycliques en C_6-C_{10}, les groupes mercapto, les groupes alkylthio en C_1-C_6, les groupes arylthio carbocycliques en C_6-C_{10}, les groupes alkylsulfonyle en C_1-C_6, les groupes arylsulfonyle carbocycliques en C_6-C_{10} et les groupes hétérocycliques ayant de 5 à 14 atomes formant le cycle, dont 1 à 5 sont des hétéro-atomes d'azote et/ou de soufre et/ou d'oxygène, lesdits groupes hétérocycliques étant non substitués ou ayant au moins un des substituants (a) et/ou (b), avec un composé de formule (IIIa) :

R^1-A-C(=Y)-$COOR^2$ (IIIa)

(dans laquelle R^1 et A sont comme définis ci-dessus ; Y représente un atome d'hydrogène et un atome d'halogène ou un groupe sulfonyloxy ou, lorsque la condensation est effectuée dans des conditions réductrices, un atome d'oxygène unique ; et R^2 est comme défini peur R^4 ci-dessus et est semblable à R^4 ou différent et facultativement une ou plusieurs des réactions de déprotection, estérification et salification.

2. Procédé selon la revendication 1, dans lequel on prépare un composé de formule (Ia) :



(Ia)

dans laquelle R^1, R^2, R^3, R^4, A, B et n sont comme définis dans la revendication 1.

3. Procédé selon la revendication 2, dans lequel R^2 représente un atome d'hydrogène ; un groupe alkyle à chaîne droite ou ramifiée ayant de 1 à 6 atomes de carbone ; un groupe aralkyle ; ou un groupe protecteur qui permet la conversion facile du groupe carboxy protégé en un groupe carboxy libre dans l'organisme vivant.

4. Procédé selon la revendication 2, dans lequel R^2 représente un atome d'hydrogène ou un groupe méthyle, éthyle, propyle, isopropyle, butyle, isobutyle, pentyle, hexyle, benzyle, acétoxyméthyle, pivaloyloxyméthyle, phtalidyle, 1-(éthoxycarbonyloxy)éthyle ou (5-méthyl-2-oxo-1,3-dioxolène-4-yl)-méthyle.

5. Procédé selon l'une quelconque des revendications 2 à 4, dans lequel R^4 représente un groupe tert-butyle, méthoxyméthyle, 2,2,2-trichloroéthyle, benzyle, p-méthoxybenzyle, diphénylméthyle, acétoxy-méthyle, pivaloyloxyméthyle, 1-(éthoxycarbonyloxy)éthyle, phtalidyle ou (5-méthyl-2-oxo-1,3-dioxolène-4-yl)méthyle.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel :
R^1-A- représente un groupe alkyle à chaîne droite ou ramifiée ayant de 4 à 9 atomes de carbone ; un groupe cycloalkyléthyle dont la partie cycloalkyle a 5 ou 6 atomes de carbone formant le cycle ; un groupe aralkyle ayant au total de 7 à 12 atomes de carbone ; un groupe phénoxyméthyle ; un groupe phénylthiométhyle ; un groupe 2-(2-thiényl)éthyle ; un groupe 2-(2-imidazolyl)éthyle ; ou un groupe 2-(2-thiazolyl)éthyle ;
R^3 représente un groupe alkyle à chaîne droite ou ramifiée ayant de 1 à 6 atomes de carbone ; un groupe cycloalkyle ayant 5 ou 6 atomes de carbone formant le cycle ; un groupe aralkyle ayant au total 7 à 11 atomes de carbone ; un groupe aryle ; un groupe hétérocyclylméthyle ; ou un groupe hétérocyclique ;
B représente un groupe méthylène ; et
n est 2 ou 3.

7. Procédé selon la revendication 2, dans lequel :
R^1 représente un groupe alkyle en C_4-C_7, un groupe cycloalkyle en C_5 ou C_6, un groupe phényle ou un groupe phényle ayant au moins un des substituants (a) et/ou (b) ;
R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_4 ou un groupe benzyle ;
R^3 représente un groupe alkyle en C_3-C_6, un groupe phényle ou un groupe phényle ayant au moins un des substituants (a) et/ou (b) ;
R^4 représente un atome d'hydrogène, un groupe alkyle en C_1-C_4, un groupe benzyle, un groupe p-méthoxybenzyle ou un groupe diphénylméthyle ;
A représente un groupe alkylène en C_1 ou C_2 ;
B représente un groupe méthylène ; et
n est 2.

8. Procédé selon la revendication 2, dans lequel :
R^1 représente un groupe butyle, un groupe pentyle, un groupe hexyle, un groupe cyclohexyle ou un groupe phényle ;
R^2 représente un atome d'hydrogène, un groupe alkyle en C_2-C_4 ou un groupe benzyle ;
R^3 représente un groupe phényle ou un groupe halogénophényle ;
R^4 représente un atome d'hydrogène, un groupe alkyle en C_2-C_4, un groupe p-méthoxybenzyle ou un groupe diphénylméthyle ;
A représente un groupe éthylène ;
B représente un groupe méthylène ; et
n est 2.

9. Procédé selon la revendication 1, dans lequel les composés réagissants et les conditions de réaction sont choisis pour préparer :
l'α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydro azépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'acide α-[3-(1-carboxy-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de

tert-butyle,
l'acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique,
l'acide α-[3-(1-carboxy-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétique,
l'α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique,
l'α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'acide α-{3(S)-[1(S)-éthoxycarbonyl-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-éthoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-butoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique, ou
l'acide α-'{(S)-[1(S)-butoxycarbonyl-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique.

10. Procédé selon l'une quenconque des revendications 1 à 9, dans lequel ledit composé de formule (IIIa) répond à la formule (III) :

R^1-A-CH($COOR^2$)-X (III)

(dans laquelle R^1, A et R^2 sont comme définis dans la revendication 1 et X représente un atome d'halogène ou un groupe sulfonyloxy).

11. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel ledit composé de formule (IIIa) répond à la formule (IV) :

R^1-A-C(= O)-$COOR^2$ (IV)

(dans laquelle R^1, A et R^2 sont comme définis dans la revendication 1) et la condensation est effectuée dans des conditions de condensation réductrices.

12. Emploi pour la fabrication d'un médicament pour le traitement de l'hypertension d'un composé de formule (I), comme défini dans la revendication 1, ou d'un sel ou ester pharmaceutiquement acceptables de celui-ci.

13. Emploi pour la fabrication d'un médicament pour le traitement de l'hypertension d'un composé de formule (Ia), comme défini dans la revendication 2, ou d'un sel pharmaceutiquement acceptable de celui-ci.

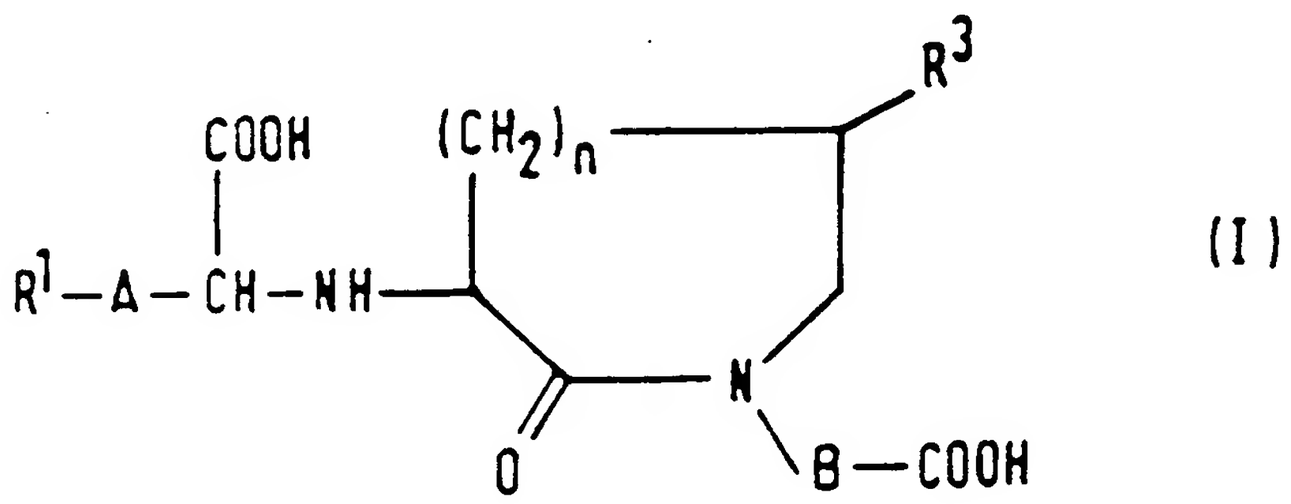
14. Emploi selon la revendication 12, dans lequel ledit composé est :
l'α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'acide α-[3-(1-carboxy-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-éthoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique,
l'acide α-[3-(1-carboxy-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétique,
l'α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]acétate de

tert-butyle,
l'acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-6-(p-fluorophényl)-2-oxoperhydroazépine-1-yl]-acétique,
l'α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétate de tert-butyle,
l'acide α-[3-(1-butoxycarbonyl-3-phénylpropylamino)-2-oxo-6-phénylperhydroazépine-1-yl]acétique,
l'acide α-{3(S)-[1(S)-éthoxycarbonyl-3-phénylpropylamino]2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl)acétique,
l'acide α-(3(S)-[1(S)-éthoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-carboxy-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique,
l'acide α-{3(S)-[1(S)-butoxycarbonyl-3-phénylpropylamino]-6(R)-(p-fluorophényl)-2-oxoperhydroazépine-1-yl}acétique, ou
l'acide α-{3(S)-[1(S)-butoxycarbonyl-3-phénylpropylamino]-2-oxo-6(R)-phénylperhydroazépine-1-yl}acétique.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, LI, LU, NL, SE

1. Verbindungen der Formel (I)

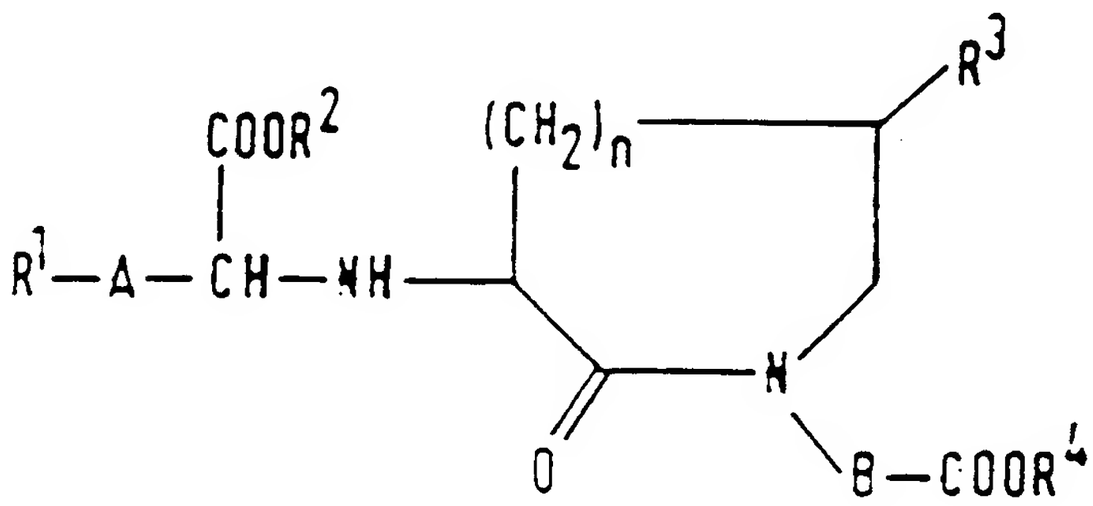


(I)

in welcher
R^1 eine C_1-C_{10}-Alkylgruppe, eine C_3-C_8-Cycloalkylgruppe, eine C_6-C_{14}-Arylgruppe oder eine heterocyclische Gruppe mit 4 bis 14 Ringatomen, von welchen 1 bis 5 von Stickstoff und/oder Sauerstoff und/oder Schwefel gebildete Heteroatome sind, bedeutet, wobei die erwähnte Alkylgruppe zumindest einen der Substituenten (a) besitzt oder die erwähnte Cycloalkylgruppe, Arylgruppe oder heterocyclische Gruppe zumindest einen der Substituenten (a) und/oder (b) aufweist,
R^3 eine C_1-C_{10}-Alkylgruppe, eine C_3-C_8-Cycloalkylgruppe, eine Aralkylgruppe mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocyclisichen C_6-C_{10}-Arylgruppe als Arylteil, eine C_6-C_{14}-Arylgruppe, eine C_1-C_6-Alkylgruppe mit einem heterocyclischen Substituenten oder eine heterocyclische Gruppe darstellt, wobei die erwähnte heterocyclische Gruppe oder der erwähnte heterocyclische Substituent 4 bis 14 Ringatome aufweist, von welchen 1 bis 5 von Stickstoff und/oder Sauerstoff und/oder Schwefel gebildete Heteroatome sind, oder die erwähnte Alkylgruppe zumindest einen der Substituenten (a) besitzt oder die erwähnte Cycloalkylgruppe, Arylgruppe oder heterocyclische Gruppe zumindest einen der Substituenten (a) und/oder (b) aufweist,
A eine Einfachbindung, eine Methylengruppe, eine Äthylengruppe oder eine Gruppe der Formel -CO-CH_2-, -O-CH_2- oder -S-CH_2- darstellt,
B eine Alkylengruppe mit 1 bis 4 Kohlenstoffatomen bedeutet und
n eine ganze Zahl von 1 bis 3 ist,
wobei
die Substituenten (a)
Hydroxygruppen, C_1-C_6-Alkoxygruppen, carbocyclische C_6-C_{10}-Arylgruppen mit 0 bis 3 der Substituenten (a) und/oder (b), Aralkyloxygruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocycli-

schen C_6-C_{10}-Arylgruppe als 0 bis 3 der Substituenten (a) und/oder (b) aufweisenden Arylteil, C_6-C_{10}-Aryloxygruppen, Halogenatome, Nitrogruppen, Cyanogruppen, Carboxygruppen, Alkoxycarbonylgruppen mit inspesamt 2 bis 7 Kohlenstoffatomen, Aminogruppen, C_1-C_6-Alkylaminogruppen, Dialkylaminogruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, von aliphatischen oder carbocyclischen aromatischen Carbonsäuren abgeleitete Acylaminogruppen, Carbamoylgruppen, Alkylcarbamoylgruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil, Dialkylcarbamoylgruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, Mercaptogruppen, C_1-C_6-Alkylthiogruppen, carbocyclische C_6-C_{10}Arylthiogruppen, C_1-C_6-Alkylsulfonylgruppen und carbocyclische C_6-C_{10}-Arylsulfonylgruppen mit 0 bis 3 C_1-C_6-Alkylsubstituenten im Arylteil sind und
die Substituenten (b)
C_1-C_6-Alkylgruppen und Aralkylgruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocyclischen C_6-C_{10}-Arylgruppe mit 0 bis 3 der Substituenten (a) und/oder (b) als Arylteil sind,
und pharmazeutisch annehmbare Salze und Ester hievon.

2. Verbindungen der Formel (Ia)



(Ia)

worin R^1, R^3, A, B und n die in Anspruch 1 angegebene Bedeutung besitzen und die untereinander gleichen oder voneinander verschiedenen Reste R^2 und R^4 je für sich ein Wasserstoffatom, eine C_1-C_{10}-Alkylgruppe, eine Aralkylgruppe mit einer unsubstituierten oder in der unten unter (c) definierten Weise substituierten carbocyclischen C_6-C_{10}-Arylgruppeals Arylteil und einer C_1-C_6-Alkylgruppe als Alkylteil, eine carbocyclische C_6-C_{14}-Arylgruppe, eine Phthalidylgruppe oder eine substituierte Silylgruppe bedeuten, wobei die von R^2 und R^4 gebildeten Gruppen unsubstituiert sind oder zumindest einen aus
(c) C_1-C_6-Alkylgruppen außer im Falle einer von einer Alkylgruppe gebildeten Stammgruppe, Halogenatomen, Hydroxygruppen, C_1-C_6-Alkoxygruppen, durch eine C_1-C_6-Alkoxygruppe substituierten C_1-C_3-Alkoxygruppen, von einer aliphatischen und aromatischen carbocyclischen Carbonsäure abgeleiteten Acyloxygruppen, Oxogruppen, Carboxygruppen, Alkoxycarbonylgruppen mit einer C_1-C_6-Alkoxygruppe als Alkoxyteil, Alkoxycarbonyloxygruppen mit einer C_1-C_6-Alkoxygruppe als Alkoxyteil, von einer aliphatischen und carbocyclischen aromatischen Carbonsäure abgeleiteten Acylaminogruppen, Nitrogruppen, Cyanogruppen, Aminogruppen, C_1-C_6-Alkylaminogruppen, Dialkylaminogruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, carbocyclischen C_6-C_{10}-Arylaminogruppen, Mercaptogruppen, C_1-C_6-Alkylthiogruppen, carbocyclischen C_6-C_{10}-Arylthiogruppen, C_1-C_6-Alkylsulfonylgruppen, carbocyclischen C_6-C_{10}-Arylsulfonylgruppen und heterocyclischen Gruppen mit 5 bis 14 Ring-Atomen, von welchen 1 bis 5 von Stickstoff und/oder Schwefel und/oder Sauerstoff gebildete Heteroatome sind, ausgewählten Substituenten aufweisen, wobei die heterocyclischen Gruppen unsubstituiert sind oder zumindest einen der Substituenten (a) und/oder (b) besitzen.

3. Verbindungen nach Anspruch 2, worin R^2 ein Wasserstoffatom, eine geradkettige oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Aralkylgruppe oder eine Schutzgruppe darstellt, welche die geschützte Carboxygruppe im lebenden Körper leicht in eine freie Carboxygruppe umwandelbar macht.

4. Verbindungen nach Anspruch 2, worin R^2 ein Wasserstoffatom oder eine Methyl-, Äthyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, Pentyl-, Hexyl-, Benzyl-, Acetoxymethyl-, Pivaloyloxymethyl-, Phthalidyl-, 1-

(Äthoxycarbonyloxy)äthyl- oder (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methylgruppe darstellt.

5. Verbindungen nach irgendeinem der Ansprüche 2 bis 4, worin R^4 eine t-Butyl-, Methoxymethyl-, 2,2,2-Trichloräthyl-, Benzyl-, p-Methoxybenzyl-, Diphenylmethyl-, Acetoxymethyl-, Pivaloyloxymethyl-, 1-(Äthoxycarbonyloxy)äthyl-Phthalidyl- oder (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methylgruppe darstellt.

6. Verbindungen nach irgendeinem der Ansprüche 1 bis 5, worin
R^1-A- eine geradkettige oder verzweigtkettige Alkylgruppe mit 4 bis 9 Kohlenstoffatomen, eine Cycloalkyläthylgruppe mit 5 oder 6 Ringkohlenstoffatomen im Cycloalkylteil, eine Aralkylgruppe mit insgesamt 7 bis 12 Kohlenstoffatomen, eine Phenoxymethylgruppe, eine Phenylthiomethylgruppe, eine 2-(2-Thienyl)äthylgruppe, eine 2-(2-Imidazolyl)äthylgruppe oder eine 2-(2-Thiazolyl)äthylgruppe darstellt,
R^3 eine geradkettige oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Cycloalkylgruppe mit 5 oder 6 Ringkohlenstoffatomen, eine Aralkylgruppe mit insgesamt 7 bis 11 Kohlenstoffatomen, eine Arylgruppe, eine Heterocyclylmethylgruppe oder eine heterocyclische Gruppe bedeutet,
B für eine Methylengruppe steht und
n gleich ist 2 oder 3.

7. Verbindungen nach Anspruch 2, worin
R^1 eine C_4-C_7-Alkylgruppe, eine C_5- oder C_6-Cycloalkylgruppe, eine Phenylgruppe oder eine Phenylgruppe mit zumindest einem aus den Substituenten (a) und den Substituenten (b) ausgewählten Substituenten darstellt,
R^2 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine Benzylgruppe bedeutet,
R^3 für eine C_3-C_6-Alkylgruppe, eine Phenylgruppe oder eine Phenylgruppe mit zumindest einem aus den Substituenten (a) und den Substituenten (b) ausgewählten Substituenten steht,
R^4 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe, eine Benzylgruppe, eine p-Methoxybenzylgruppe oder eine Diphenylmethylgruppe bedeutet,
A eine C_1- oder C_2-Alkylengruppe darstellt,
B für eine Methylengruppe steht und
n gleich ist 2.

8. Verbindungen nach Anspruch 2, worin
R^1 eine Butylgruppe, eine Pentylgruppe, eine Hexylgruppe, eine Cyclohexylgruppe oder eine Phenylgruppe darstellt,
R^2 ein Wasserstoffatom, eine C_2-C_4-Alkylgruppe oder eine Benzylgruppe bedeutet,
R^3 für eine Phenylgruppe oder eine Halogenphenylgruppe steht,
R^4 ein Wasserstoffatom, eine C_2-C_4-Alkylgruppe, eine p-Methoxybenzylgruppe oder eine Diphenylmethylgruppe bedeutet,
A für eine Äthylengruppe steht,
B eine Methylengruppe bedeutet und
n gleich ist 2.

9. t-Butyl-{α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetat}.

10. α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure.

11. α-[3-(1-Carboxy-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure.

12. t-Butyl-{α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-acetat}.

13. α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure.

14. α-[3-(1-Carboxy-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure.

15. t-Butyl-{α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-acetat}.

16. α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure.

17. t-Butyl-{α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetat}.

18. α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure.

19. α-{3(S)-[1(S)-Äthoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure.

20. α-(3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure.

21. α-(3(S)-[1(S)-Äthoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure.

22. α-{3(S)-{1(S)-Carboxy-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essig säure.

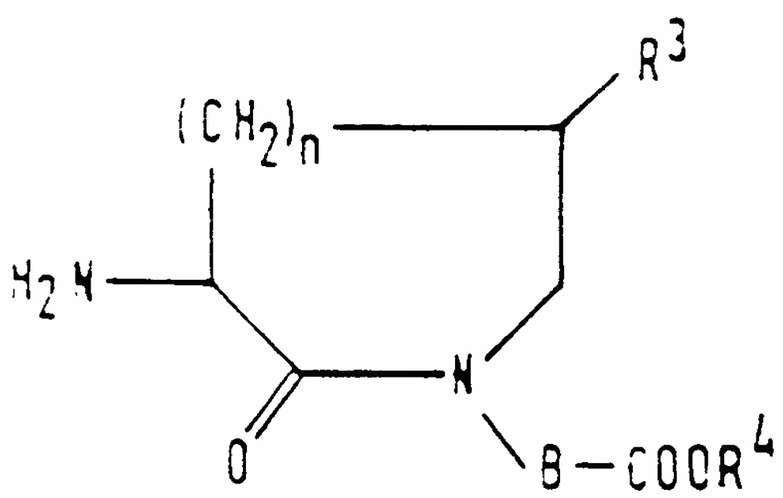
23. α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure.

24. α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure.

25. Pharmazeutische Mischung zum Behandeln von durch Angiotensin bewirkter Hypertension, welche Mischung ein hypotensives Mittel im Gemisch mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel enthält, worin das hypotensive Mittel zumindest eine der in irgendeinem der vorhergehenden Ansprüche beanspruchte Verbindung ist.

26. Verwendung eines in irgendeinem der Ansprüche 1 bis 24 beanspruchten Verbindung zum Herstellen eines Heilmittels zum Behandeln von durch Angiotensin bewirkter Hypertension.

27. Verfahren zum Herstellen einer in irgendeinem der Ansprüche 1 bis 24 beanspruchten Verbindung, bei welchem Verfahren eine Verbindung der allgemeinen Formel (II)



(II)

(in welcher R^3, B und n die in Anspruch 1 angegebene Bedeutung besitzen und R^4 so wie in Anspruch 2 definiert ist) mit einer Verbindung der Formel (IIIa)

R^1-A-C(=Y)-COOR^2 (IIIa)

kondensiert wird (in welcher R^1 und A die in Anspruch 1 angegebene Bedeutung besitzen, Y ein Wasserstoffatom und ein Halogenatom oder eine Sulfonyloxygruppe bedeutet oder, falls die Kondensation unter reduzierenden Bedingungen vorgenommen wird, ein einziges Sauerstoffatom bedeutet und R^2 die in Anspruch 2 angegebene Bedeutung besitzt), worauf gegebenenfalls eine oder mehrere der Umsetzungen Abspalten von Schutzgruppen, Verestern und Herstellen eines Salzes vorgenommen werden.

28. Verfahren nach Anspruch 27, worin die Verbindung der Formel (IIIa) die Formel (III)

R^1-A-CH(COOR^2)-X (III)

besitzt, (in welcher R^1, A und R^2 die in Anspruch 27 angegebene Bedeutung besitzt und X ein Halogenatom oder eine Sulfonyloxygruppe darstellt).

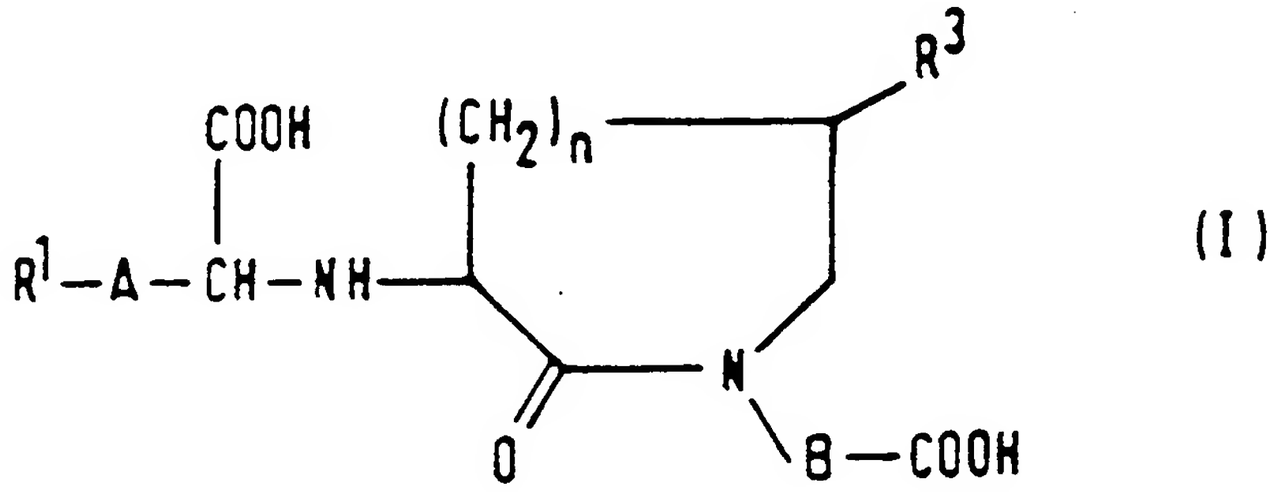
29. Verfahren nach Anspruch 27, worin die Verbindung der Formel (IIIa) die Formel (IV)

R^1-A-C(= O)-COOR^2 (IV)

besitzt (in welcher R^1, A und R^2 die in Anspruch 27 angegebene Bedeutung besitzen) und die Kondensation unter reduzierenden Kondensationsbedingungen vorgenommen wird.

Patentansprüche für folgende Vertragsstaaten : AT, ES

1. Verfahren zum Herstellen einer Verbindung der Formel (I)



(I)

in welcher

R^1 eine C_1-C_{10}-Alkylgruppe, eine C_3-C_8-Cycloalkylgruppe, eine C_6-C_{14} -Arylgruppe oder eine heterocyclische Gruppe mit 4 bis 14 Ringatomen, von welchen 1 bis 5 von Stickstoff und/oder Sauerstoff und/oder Schwefel gebildete Heteroatome sind, bedeutet, wobei die erwähnte Alkylgruppe zumindest einen der Substituenten (a) besitzt oder die erwähnte Cycloalkylgruppe, Arylgruppe oder heterocyclische Gruppe zumindest einen der Substituenten (a) und/oder (b) aufweist,

R^3 eine C_1-C_{10}-Alkygruppe, eine C_3-C_8-Cycloalkylgruppe, eine Aralkylgruppe mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocyclischen C_6-C_{10}-Arylgruppe als Arylteil, eine C_6-C_{14}-Arylgruppe, eine C_1-C_6-Alkylgruppe mit einem heterocyclischen Substituenten oder eine heterocyclische Gruppe darstellt, wobei die erwähnte heterocyclische Gruppe oder der erwähnte heterocyclische Substituent 4 bis 14 Ringatome aufweist, von welchen 1 bis 5 von Stickstoff und/oder Sauerstoff und/oder Schwefel gebildete Heteroatome sind, oder die erwähnte Alkylgruppe zumindest einen der Substituenten (a) besitzt oder die erwähnte Cycloalkylgruppe, Arylgruppe oder heterocyclische Gruppe zumindest einen der Substituenten (a) und/oder (b) aufweist,

A eine Einfachbindung, eine Methylengruppe, eine Äthylengruppe oder eine Gruppe der Formel -CO-CH_2-, -O-CH_2- oder -S-CH_2- darstellt,

B eine Alkylengruppe mit 1 bis 4 Kohlenstoffatomen bedeutet und

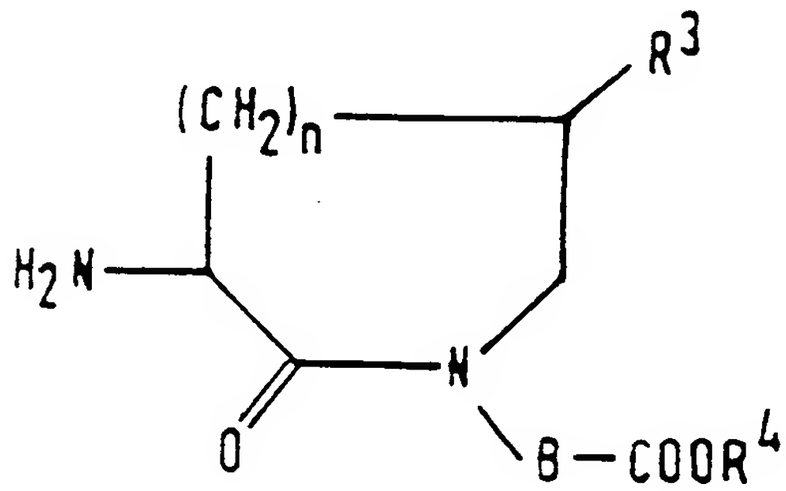
n eine ganze Zahl von 1 bis 3 ist,

wobei

die Substituenten (a)

Hydroxygruppen, C_1-C_6-Alkoxygruppen, carbocyclische C_6-C_{10}-Arylgruppen mit 0 bis 3 der Substituenten (a) und/oder (b), Aralkyloxygruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocyclischen C_6-C_{10}-Arylgruppe als 0 bis 3 der Substituenten (a) und/oder (b) aufweisendem Arylteil, C_6-C_{10}-Aryloxygruppen, Halogenatome, Nitrogruppen, Cyanogruppen, Carboxygruppen, Alkoxycarbonylgruppen mit insgesamt 2 bis 7 Kohlenstoffatomen, Aminogruppen, C_1-C_6-Alkylaminogruppen, Dialkylaminogruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, von aliphatischen oder carbocyclischen aromatischen Carbonsäuren abgeleitete Acylaminogruppen, Carbamoylgruppen, Alkylcarbamoylgruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil, Dialkylcarbamoylgruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, Mercaptogruppen, C_1-C_6-Alkylthiogruppen, carbocyclische C_6-C_{10}-Arylthiogruppen, C_1-C_6-Alkylsulfonylgruppen und carbocyclische C_6-C_{10}-Arylsulfonylgruppen mit 0 bis 3 C_1-C_6-Alkylsubsti-

tuenten im Arylteil sind und
die Substituenten (b)
C_1-C_6-Alkylgruppen und Aralkylgruppen mit einer C_1-C_6-Alkylgruppe als Alkylteil und einer carbocyclischen C_6-C_{10}-Arylgruppe mit 0 bis 3 Substituenten (a) und/oder (b) im Arylteil sind,
oder eines pharmazeutisch annehmbaren Salzes oder Esters hievon,
bei welchem Verfahren eine Verbindung der Formel (II)



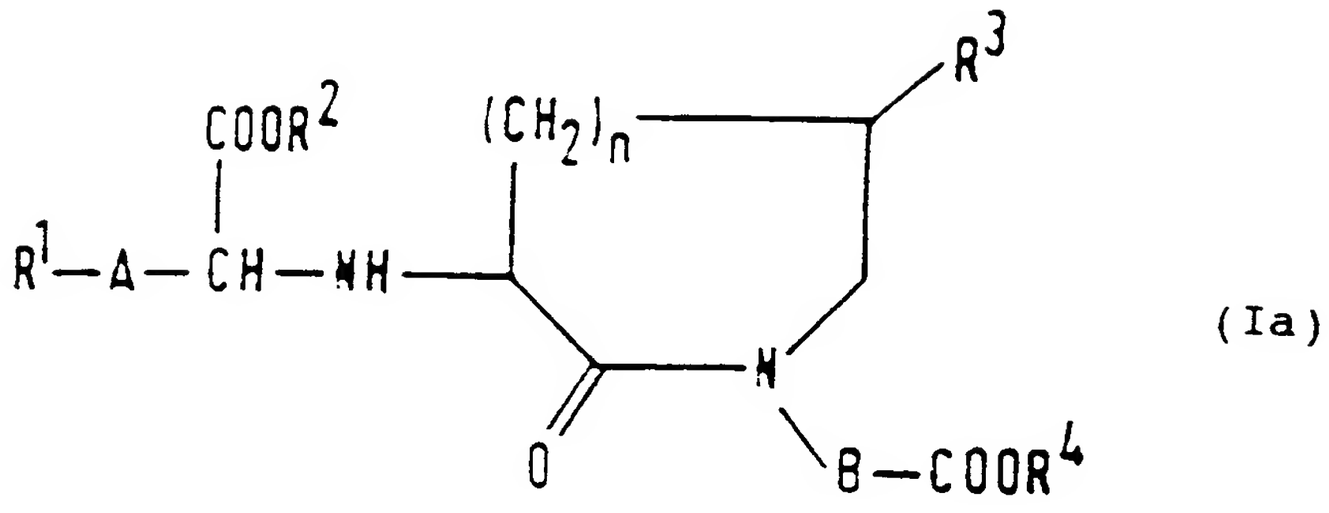
(II)

(in welcher R^3, B und n die oben angegebene Bedeutung besitzen und R^4 ein Wasserstoffatom, eine C_1-C_{10}-Alkylgruppe, eine Aralkylgruppe mit einer unsubstituierten oder in der unten unter (c) definierten Weise substituierten carbocyclischen C_6-C_{10}-Arylgruppe als Arylteil und einer C_1-C_6-Alkylgruppe als Alkylteil, eine carbocyclische C_6-C_{14}-Arylgruppe, eine Phthalidylgruppe oder eine substituierte Silylgruppe bedeutet, wobei die von R^4 gebildete Gruppe unsubstituiert ist oder zumindest einen aus
(c) C_1-C_6-Alkylgruppen außer im Falle einer von einer Alkylgruppe gebildeten Stammgruppe, Halogenatomen, Hydroxygruppen, C_1-C_6-Alkoxygruppen, durch eine C_1-C_6-Alkoxygruppe substituierten C_1-C_3-Alkoxygruppen, von einer aliphatischen und aromatischen carbocyclischen Carbonsäure abgeleitete Acyloxygruppen, Oxogruppen, Carboxygruppen, Alkoxycarbonylgruppen mit einer C_1-C_6-Alkoxygruppe als Alkoxyteil, Alkoxycarbonyloxygruppen mit einer C_1-C_6-Alkoxygruppe als Alkoxyteil, von einer aliphatischen und carbocyclischen aromatischen Carbonsäure abgeleiteten Acylaminogruppen, Nitrogruppen, Cyanogruppen, Aminogruppen, C_1-C_6-Alkylaminogruppen, Dialkylaminogruppen mit einer C_1-C_6-Alkylgruppe für jeden Alkylteil, carbocyclischen C_6-C_{10}-Arylaminogruppen, Mercaptogruppen, C_1-C_6-Alkylthiogruppen, carbocyclischen C_6-C_{10}-Arylthiogruppen, C_1-C_6-Alkylsulfonylgruppen, carbocyclischen C_6-C_{10}-Arylsulfonylgruppen und heterocyclischen Gruppen mit 5 bis 14 Ring-Atomen, von welchen 1 bis 5 von Stickstoff und/oder Schwefel und/oder Sauerstoff gebildete Heteroatome sind, ausgewählten Substituenten aufweist, wobei die heterocyclischen Gruppen unsubstituiert sind oder zumindest einen der Substituenten (a) und/oder (b) besitzen) mit einer Verbindung der Formel (IIIa)

R^1-A-C(=Y)-COOR^2 (IIIa)

(in welcher R^1 und A die oben angegebene Bedeutung besitzen, Y ein Wasserstoffatom und ein Halogenatom oder eine Sulfonyloxygruppe oder, falls die Kondensation unter reduzierenden Bedingungen vorgenommen wird, ein einziges Sauerstoffatom bedeutet und R^2 die für R^4 angegebene Bedeutung besitzt und die gleiche Bedeutung oder eine andere Bedeutung wie R^4 hat) kondensiert wird und gegebenenfalls eine oder mehrere der Umsetzungen Abspalten von Schutzgruppen, Verestern und Salzbildung vorgenommen werden.

2. Verfahren nach Anspruch 1, worin eine Verbindung der Formel (Ia)



(Ia)

hergestellt wird, in welcher R^1 R^2, R^3, R^4, A, B und n die in Anspruch 1 angegebene Bedeutung besitzen.

3. Verfahren nach Anspruch 2, worin R^2 ein Wasserstoffatom, eine geradkettige oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Aralkylgruppe oder eine Schutzgruppe darstellt, welche die geschützte Carboxygruppe im lebenden Körper leicht in eine freie Carboxygruppe umwandelbar macht.

4. Verfahren nach Anspruch 2, worin R^2 ein Wasserstoffatom oder eine Methyl-, Athyl-, Propyl-, Isopropyl-, Butyl-, Isobutyl-, Pentyl-, Hexyl-, Benzyl-, Acetoxymethyl-, Pivaloyloxymethyl-, Phthalidyl-, 1-(Äthoxycarbonyl-oxy)äthyl- oder (5-Methyl-2-oxo-1,3-dioxolen-4-yl)methylgruppe bedeutet.

5. Verfahren nach irgendeinem der Ansprüche 2 bis 4, worin R^4 eine t-Butyl-, Methoxymethyl-, 2,2,2-Trichloräthyl-, Benzyl-, p-Methoxybenzyl-, Diphenylmethyl-, Acetoxymethyl-, Pivaloyloxymethyl-, 1-(Äthoxycarbonyloxy)äthyl-, Phthalidyl- oder (5-Methyl-2-oxo-1,3-dioxolen-4yl)methylgruppe bedeutet.

6. Verfahren nach irgendeinem der Ansprüche 1 bis 5, worin
R^1-A- eine geradkettige oder verzweigtkettige Alkylgruppe mit 4 bis 9 Kohlenstoffatomen, eine Cycloalkyläthylgruppe mit 5 oder 6 Ringkohlenstoffatomen im Cycloalkylteil, eine Aralkylgruppe mit insgesamt 7 bis 12 Kohlenstoffatomen, eine Phenoxymethylgruppe, eine Phenylthiomethylgruppe, eine 2-(2-Thienyl)äthylgruppe, eine 2(2-Imidazolyl)äthylgruppe oder eine 2(2-Thiazolyl)äthylgruppe darstellt,
R^3 eine geradkettige oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Cycloalkylgruppe mit 5 oder 6 Ringkohlenstoffatomen, eine Aralkylgruppe mit insgesamt 7 bis 11 Kohlenstoffatomen, eine Arylgruppe, eine Heterocyclylmethylgruppe oder eine heterocyclische Gruppe bedeutet,
B für eine Methylengruppe steht und
n gleich ist 2 oder 3.

7. Verbindungen nach Anspruch 2, worin
R^1 eine C_4-C_7-Alkylgruppe, eine C_5- oder C_6-Cycloalkylgruppe, eine Phenylgruppe oder eine Phenylgruppe mit zumindest einem aus den Substituenten (a) und/oder en Substituenten (b) ausgewählten Substituenten darstellt,
R^2 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe oder eine Benzylgruppe bedeutet,
R^3 für eine C_3-C_6-Alkylgruppe, eine Phenylgruppe oder eine Phenylgruppe mit zumindest einem aus den Substituenten (a) und/oder den Substituenten (b) ausgewählten Substituenten steht,
R^4 ein Wasserstoffatom, eine C_1-C_4-Alkylgruppe, eine Benzylgruppe, eine p-Methoxybenzylgruppe oder eine Diphenylmethylgruppe bedeutet,
A eine C_1- oder C_2-Alkylengruppe darstellt,
B für eine Methylengruppe steht und
n gleich ist 2.

8. Verfahren nach Anspruch 2, worin
R^1 eine Butylgruppe, eine Pentylgruppe, eine Hexylgruppe, eine Cyclohexylgruppe oder eine Phenylgruppe darstellt,
R^2 ein Wasserstoffatom, eine C_2-C_4-Alkylgruppe oder eine Benzylgruppe bedeutet,

R^3 für eine Phenylgruppe oder eine Halogenphenylgruppe steht,
R^4 ein Wasserstoffatom, eine C_2-C_4-Alkylgruppe, eine p-Methoxybenzylgruppe oder eine Diphenylmethylgruppe bedeutet,
A für eine Äthylengruppe steht,
B eine Methylengruppe bedeutet und
n gleich ist 2.

9. Verfahren nach Anspruch 1, worin die Reaktionsteilnehmer und Umsetzungsbedingungen so gewählt werden, daß
t-Butyl-{α-[3-(1-äthoxycarbonyl-3-phenylpropylamino)-2-oxo-6-Phenylperhydroazepin-1-yl]acetat};
α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure;
α-[3-(1-Carboxy-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-acetat};
α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
α-[3-(1-Carboxy-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-essigsäure;
α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetat};
α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure;
α-{3(S)-[1(S)-Äthoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure;
α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure;
α-{3(S)-[1(S)-Äthoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure;
α-{3(S)-[1(S)-Carboxy-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure;
α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl)-essigsäure;
oder
α-{3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl]essigsäure
hergestellt wird.

10. Verfahren nach irgendeinem der Ansprüche 1 bis 9, worin die Verbindung der Formel (IIIa) die Formel (III)

$$R^1\text{-A-CH(COOR}^2\text{)-X} \qquad \text{(III)}$$

(in welcher R^1, A und R^2 die in Anspruch 1 angegebene Bedeutung besitzen und X ein Halogenatom oder eine Sulfonyloxygruppe darstellt) besitzt.

11. Verfahren nach irgendeinem der Ansprüche 1 bis 9, worin die Verbindung der Formel (IIIa) die Formel (IV)

$$R^1\text{-A-C(=O)-COOR}^2 \qquad \text{(IV)}$$

(in welcher R^1, A und R^2 die in Anspruch 1 angegebene Bedeutung besitzen) besitzt und die Kondensation unter reduzierenden Kondensationsbedingungen durchgeführt wird.

12. Verwendung einer in Anspruch 1 definierten Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salzes oder Esters hievon zum Herstellen eines Heilmittels zum Behandeln von Hypertension.

13. Verwendung einer in Anspruch 2 definierten Verbindung der Formel (Ia) oder eines pharmazeutisch annehmbaren Salzes hievon zum Herstellen eines Heilmittels zum Behandeln von Hypertension.

14. Verwendung nach Anspruch 12, worin die Verbindung
t-Butyl-{α-[3-(1-äthoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetat};
α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-2-OXO-6-phenylperhydroazepin-1-yl]essigsäure;

α-[3-(1-Carboxy-3-phenylpropylamIno)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-acetat};
α-[3-(1-Äthoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
α-[3-(1 = Carboxy-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-bucoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]-acetat};
α-[3-(1-Butoxycarbonyl-3-phenylpropylamino)-6-(p-fluorphenyl)-2-oxopehydroazepin-1-yl]essigsäure;
t-Butyl-{α-[3-(1-butoxycarbonyl-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]acetat};
α-[3-(1-Butoxycarbony1-3-phenylpropylamino)-2-oxo-6-phenylperhydroazepin-1-yl]essigsäure;
α-{3(S)-[1(S)-Äthoxycarbonyl-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl]essigsäure;
α-(3(S)-[1(S)-Carboxy-3-phenylpropylamino]-2-oxo-6(R)-phenylperhydroazepin-1-yl}essigsäure;
α-(3(S)-[1(S)-Äthoxycarbonyl-3-pnenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure;
α-(3(S)-[1(S)-Carboxy-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl]essigsäure;
α-[3(S)-[1(S)-Butoxycarbonyl-3-phenylpropylamino]-6(R)-(p-fluorphenyl)-2-oxoperhydroazepin-1-yl}essigsäure;
oder
α-{3(S)-{1(S)-Butoxycarbonyl-3-phenylpropylaminol-2-oxo-6(R)-phenylperhydroazepin-1-yl)essigsäure
ist.